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THE NATURAL HISTORY OF UNCOMPLICATED SYPHILITIC AORTITIS

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THE pathologic change of aortic dilatation has been commented upon since the time of Paré in the sixteenth century. The relation of this dilatation to syphilis was strongly suspected early, but it was finally proved in 1906 when Reuter[1] demonstrated spirochetes in the aorta. However, it was not until later that the diagnosis of uncomplicated aortitis received much clinical attention. In 1913, Longcope[2] reviewed sixty-seven cases of aortic syphilis proved at autopsy, twelve with uncomplicated aortitis. In discussing his patients, he grouped aortic insufficiency and aneurysm with aortitis so that his conclusions regarding prognosis were not applicable to aortitis alone.

In 1932, the first successful attempt to outline criteria for the diagnosis of uncomplicated aortitis was presented by Moore, Danglade, and Reisinger.[3] They reviewed the cases of 105 patients with syphilitic aortitis proved at autopsy and without aortic insufficiency or aneurysm in an effort to find out which signs and symptoms were of value in making the diagnosis. Their patients were predominantly Negro men less than 50 years of age. They found that the signs and symptoms most useful in making the diagnosis of aortitis were: (1) aortic widening as indicated by roentgenogram, (2) increased retromanubrial dullness, (3) evidence of circulatory embarrassment, (4) accentuated or tambourlike second aortic sound, (5) indications of progressive failure, (6) substernal pain, and (7) paroxysmal dyspnea. They suggested that a positive diagnosis could be made if any four of these signs or symptoms were present. They felt that a diagnosis could have been made in 50 per cent of their patients by using these criteria, whereas it had actually been made clinically in only four patients and suspected in three others. No statement was found in their paper regarding the

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presence of hypertension or other cardiac disease, and there was no indication as to whether or not patients with coronary ostial stenosis were included. That they may have been was indicated by their description of aortitis "with its associated secondary cardiac changes of hypertrophy and chronic myocarditis."

With the exception of those dealing with symptoms, the diagnostic criteria set forth by Moore and associates[3] have been widely accepted by subsequent authors. Keefer and Resnick[4] previously had studied the records of eighty-three patients with aortitis proved at autopsy and had found that in all cases where paroxysmal dyspnea was noted, other cardiovascular disease, such as aortic insufficiency, arteriosclerosis, or hypertension, was present. Wilson[5] found the symptoms of failure or pain to be a result of either coronary ostial stenosis or concomitant hypertension or arteriosclerotic coronary artery disease. Maynard[6] studied fifty-nine cases of syphilitic aortitis diagnosed clinically. He did not find symptoms to be of value in making the diagnosis. His criteria were: (1) a patient with proved syphilis under 40 years of age, (2) no hypertension or arteriosclerosis, (3) x-ray evidence of dilated aorta, (4) accentuated aortic second sound, and (5) aortic systolic murmur. The diagnosis of aortitis was confirmed eleven times in thirteen of his patients who came to autopsy. In this series, patients with arteriosclerosis or hypertension or those over 40 years of age were excluded because of the similarity of diagnostic signs resulting from other aortic disease.

Padget and Moore[7] reviewed the literature regarding the significance of x-ray evidence of widening of the aorta and concluded that careful interpretation of the left anterior oblique position supplemented by fluoroscopy was the most useful technique and that the anteroposterior roentgenogram was of little value in demonstrating early aortic widening. X-ray evidence of aortic widening has been elicited and considered as helpful in making the diagnosis of aortitis by other observers.[8] Angiocardiography has attracted attention as a useful tool in the diagnosis of syphilitic aortitis. Steinberg, Dotter, Peabody, Reader, Heimoff, and Webster[9] have studied its use in the diagnosis of aortitis and conclude that it is of definite value. However, they point out that hypertension will cause aortic dilatation which may be similar to that of syphilitic aortitis and that angiocardiograms may be negative if aortitis exists without aortic widening.

Recently, skepticism has been expressed regarding the feasibility of making the diagnosis of uncomplicated aortitis. Boharas, Hollander, and Goldsmith[10] studied 200 patients with syphilis and 200 patients without syphilis and found that the incidence of the diagnostic criteria of aortitis was no greater in one group than in the other. Kampmeier, Glass, and Fleming[11] reviewed thirty-three autopsy proved cases of aortitis. They found that over one-half of the patients were more than 50 years of age, that sixteen presented no signs or symptoms of aortitis, and that the diagnosis was correctly made in only one patient. Both of these groups of authors concluded that the clinical diagnosis of syphilitic aortitis could not be made accurately.

MATERIAL

The patients presented in this series differ from most other groups in that they were all diagnosed clinically. Patients whose aortitis was not discovered

until post-mortem examination are excluded, but those patients in whom the diagnosis of aortitis was made, though it was later found to be incorrect, were included.

All patients in whom a diagnosis of uncomplicated syphilitic aortitis was made at the New York Hospital between 1930 and 1950 were included. Occasionally, one medical student or junior staff member would make a diagnosis which would not be sustained by more experienced observers, and in such cases it was felt that it was not valid; but whenever the diagnosis was made by a senior staff member, or sustained by different observers, the patient was considered to have had syphilitic aortitis. It is interesting to note that almost all the cases of aortitis were diagnosed on the Medical Service of the hospital and that the great majority, having been referred because of a positive Wassermann reaction, were first diagnosed in the Syphilis Clinic. The physicians in this clinic have long been interested in the problem of aortitis and have taken particular trouble to elicit and evaluate the signs and symptoms commonly mentioned in association with this disease.

Only patients with uncomplicated syphilitic aortitis were used. Those patients were excluded in whom coronary ostial stenosis, aortic insufficiency, or saccular or fusiform aneurysm was present at the time of the original diagnosis. Patients with a small, diffuse dilatation of the aorta were classified as having aortitis, whereas if they had a more marked dilatation they were said to have a fusiform aneurysm and in consequence were excluded from this study. Unfortunately, no definite dividing line was established, and we were dependent upon the arbitrary choice of the physicians making the diagnosis. It may be said, however, that it has been the custom to reserve the diagnosis of aortitis for those patients in whom the dilatation was so slight that a definite x-ray diagnosis of fusiform dilatation was not possible. For the purposes of this study, hypertension and arteriosclerosis were considered to exist if the physicians making the diagnosis of aortitis also noted one of these other diseases, and patients with these diseases were included.

All patients having a diagnosis of syphilis in the New York Hospital are referred to the Syphilis Clinic, where they are given a thorough examination with particular attention and interest directed toward the cardiovascular system. They also receive a fluoroscopic examination, and a roentgenogram in the left anterior oblique position specifically for the evaluation of the aortic size is taken. All patients are followed indefinitely with yearly physical examinations. The majority of patients in this study have been followed until death or are currently being seen in the clinic. Every effort has been made to contact those whose attendance has lapsed. When they could not be persuaded to come to the clinic for a physical examination, reports from their private physicians have been obtained. It was impossible to determine the present status of a small number of patients.

The syphilis clinic has records of 547 patients followed for cardiovascular syphilis. Of these, 309 have aortic insufficiency, ninety-five have aneurysms, and two have coronary ostial stenosis. The remaining 141 patients with syphilitic aortitis are the subject of this report.

RESULTS

1. Similarity of Material.—Since past studies have correctly pointed out that hypertension and arteriosclerosis can cause all the changes of aortitis,[6] it was necessary that those patients with syphilitic aortitis alone be considered separately from those with other cardiovascular disease.

The marked differences of age at diagnosis, of sex, of race distribution, and of the death rate in these two groups emphasized the need to study them separately. The average age of the patients without other cardiovascular disease at the time of diagnosis was 50 years, whereas it was 54.5 years for those with hypertension or arteriosclerosis. Twenty-four per cent of the former group are now dead, whereas 46 per cent of the latter group were dead at the time of the last report. These differences are presented in detail in Table I.

TABLE I. AGE, SEX, RACE DISTRIBUTION, AND MORTALITY COMPARED IN THOSE PATIENTS WITH AND WITHOUT HYPERTENSION OR ARTERIOSCLEROSIS

	NO COMPLICATING CARDIOVASCULAR DISEASE	%	COMPLICATING CARDIOVASCULAR DISEASE	%
Total number of patients	93		48	
Average age at diagnosis	50.0		54.5	
Average number of years followed	7.6		6.6	
Age grouping at time of diagnosis				
Less than 40 years	12	13	2	4
40–50 years	35	37	10	20
51–60 years	36	39	21	44
More than 60 years	10	11	15	31
Race and sex distribution				
White male	64	69	26	54
White female	14	15	15	31
Negro male	10	11	6	12
Negro female	5	5	1	2
Dead at last report	22	24	22	46
Older than 60 years at time of death	9	41	13	59
60 years or less at time of death	13	59	9	41

2. Accuracy of Diagnosis.—The first problem in any clinical study of syphilitic aortitis must be whether or not the diagnosis can be made with reasonable accuracy. This can only be investigated in those patients in whom some event has occurred following the diagnosis which would allow one to check on the presence or absence of aortitis. Obviously, autopsy findings offer the most reliable information. It is felt that the subsequent development of other evidence of cardiovascular syphilis, either aneurysm or aortic insufficiency, also gives one a reasonable certainty that the original diagnosis of aortitis was correct. In the past few years, it has been possible to visualize the aorta by angiocardiography, and this is the third measure used to check the diagnosis, although it does not offer the same degree of accuracy as the first two. The angiocardiogram

may be normal when early aortitis is present and may show a widening of the base of the aorta due to hypertension which is easily confused with, and sometimes indistinguishable from, syphilitic aortitis.[9] However, in each case in the present series a diagnosis of syphilitic aortitis was arrived at with full information on the part of those interpreting the angiocardiogram regarding the complicating cardiovascular disease. It was felt, therefore, that, in spite of the difficulties, the angiocardiogram offered a reasonable confirmation of the diagnosis.

In five patients not suspected of having aortitis, one of whom had hypertension, the diagnosis was made solely on the basis of an angiocardiogram. These cases are not of value in checking on the accuracy of the clinical diagnosis and are excluded from further consideration.

Altogether the accuracy of diagnosis could be tested by one of the methods described in forty-six patients, nineteen of whom had hypertension or arteriosclerosis. Of these forty-six patients, nine had positive angiocardiograms. Four had positive angiocardiograms and as well developed aortic insufficiency or aneurysm. One had a negative angiocardiogram but later developed aortic insufficiency, and fifteen subsequently developed other manifestations of cardiovascular syphilis. Autopsies were done in two of these patients, demonstrating aortitis. Ten other autopsies demonstrated syphilitic aortitis. These results were all considered to confirm the original diagnosis.

In four patients, angiocardiograms were normal. Three autopsies failed to show aortitis. In these patients, the diagnosis of syphilitic aortitis was considered to be in error.

In Table II the over-all figures showing the accuracy of diagnosis in the patients in this series are summarized.

TABLE II. THE ACCURACY OF DIAGNOSIS OF SYPHILITIC AORTITIS

	NO COMPLICATING CARDIOVASCULAR DISEASE	COMPLICATING CARDIOVASCULAR DISEASE	ALL PATIENTS
Total group	93	48	141
Diagnosis tested	27	19	46
Diagnosis confirmed	24	15	39
Diagnosis in error	3	4	7

The diagnosis was made correctly thirty-nine times and was inaccurate seven times. In the group with arteriosclerosis and hypertension, the diagnosis was as accurate in those cases which could be checked as in the group without other cardiovascular disease.

3. Clinical Findings.—In an effort to determine what physical changes were observed in these patients, all the signs and symptoms referable to the cardiovascular system which occurred with any regularity were studied. These are presented in Table III. It is obvious that more than one sign was present in many cases.

TABLE III. FREQUENCY OF OCCURRENCE OF VARIOUS SIGNS AND SYMPTOMS IN 141 PATIENTS WITH SYPHILITIC AORTITIS

SIGN OR SYMPTOM	NO COMPLICATING CARDIOVASCULAR DISEASE (NO. IN WHICH SIGN PRESENT)	COMPLICATING CARDIOVASCULAR DISEASE (NO. IN WHICH SIGN PRESENT)
Widening of the aorta by roentgenogram	80	42
Accentuated second aortic sound	38	30
Aortic systolic murmur	50	28
Submanubrial dullness	32	20
Significant pain or dyspnea	1	6
Total cases	93	48

Electrocardiographic changes and cardiac enlargement were related to the degree and the duration of hypertension or arteriosclerosis and were of no value in making the diagnosis. Pain and dyspnea, when present, were considered to be related to other cardiovascular disease by the physicians making the diagnosis of aortitis except in two cases.

Pulse pressure was unremarkable in all cases. In the group without hypertension it was 50 mm. Hg or less in all but nine cases and over 75 mm. Hg only once when it was 90 mm. Hg. In the hypertensive group the pulse pressure was over 65 mm. Hg in twenty-three cases and over 100 mm. Hg seven times. This is considered to be associated with the complicating heart disease. Differences in the blood pressure in the two arms, marked pulsations in the suprasternal notch, and tracheal tug were each noted one or two times. These are probably of diagnostic significance when they occur, but were very uncommon in the patients in this group.

It may be seen from Table III that the most frequent changes found in these patients were x-ray evidence of widening of the base of the aorta and the three "cardinal signs" of aortitis, accentuated aortic second sound, submanubrial dullness, and a systolic murmur at the aortic area.

Though several signs were often considered in making the diagnosis, one was usually thought to be of central importance by the physician observing the patient. An attempt to separate those signs which were of primary diagnostic significance from the less important findings is presented in Table IV. It is evident that x-ray evidence of aortic dilatation and an accentuated second aortic sound were most often considered significant.

In forty-eight patients only one of the three cardinal signs was present. Autopsy, subsequent course, or angiography proved the diagnosis in these cases to be correct 21 times and incorrect once. In twenty-seven patients there was no sign suggesting aortitis, and the diagnosis was made because of x-ray changes alone. The subsequent course proved the diagnosis correct four times but inaccurate three times. Of the two times when the diagnosis was made on the basis of symptoms alone, it was wrong once. All three signs were present in twenty-two patients, in whom the diagnosis was correct each of the seven times it could be checked.

TABLE IV. INCIDENCE OF SIGNS LEADING TO THE DIAGNOSIS OF AORTITIS

SIGN	NO COMPLICATING CARDIOVASCULAR DISEASE	COMPLICATING CARDIOVASCULAR DISEASE
Roentgenogram: widened aortic shadow	57	26
Calcification of the aortic arch	0	1
Angiocardiogram	4	1
A_2 accentuated	15	12
Submanubrial dullness	9	6
Aortic systolic murmur	7	1
Symptoms only	1	1
Total number cases	93	48

Angiocardiography is an encouraging and valuable diagnostic tool. In the present series twenty positive angiocardiograms were taken. Five of these patients subsequently developed other evidence of cardiovascular syphilis or had aortitis proved by autopsy. Five negative angiocardiograms were done. One of these patients has since developed aortic insufficiency.

The serologic test for syphilis was positive in 125 patients. In thirty-one cases there was a titer of over 16 Kahn units and in eighty-six cases a titer of between 4 and 16 Kahn units, or the approximate equivalent in other titer systems. The serologic test for syphilis was negative in the remaining sixteen patients, although all of these gave a history of syphilis.

TABLE V. DURATION OF FOLLOW-UP IN 141 PATIENTS WITH SYPHILITIC AORTITIS

PERIOD FOLLOWED	NO COMPLICATING CARDIOVASCULAR DISEASE		COMPLICATING CARDIOVASCULAR DISEASE		ALL PATIENTS
	ALIVE	DEAD	ALIVE	DEAD	
Less than 6 months	4	1	4	2	11
6 months to 2 years	7	4	0	1	12
2 years to 5 years	10	8	6	6	30
5 years to 10 years	12	6	3	9	30
10 years to 15 years	38	3	13	4	58
Total	71	22	26	22	141

4. Course and Prognosis.—

A. Period of observation following the diagnosis of aortitis: Patients were known to be alive to the time of this report, known to be dead, or had been lost to the clinic. In the first two groups, the exact period of observation was known. In the group who were lost, the period from the time of observation until the last definite evidence that they were alive was used to measure the length of follow-up. The number of patients followed and the time they were followed are presented in Table V. One hundred and eighteen patients (77 per cent of the total) were followed for more than two years, of whom 69 per cent were living

at the time of last report. Eighty-eight patients (62 per cent) were followed for more than five years, of whom 75 per cent were living, and fifty-eight patients (41 per cent) were followed for over ten years. Of these, 88 per cent were living at the time of last report. Though the follow-up was relatively short in many cases (due to the fact that the diagnosis was made in recent years), the percentage who have died in each group is uniformly low.

B. The development of aortic insufficiency or aneurysm: Fourteen patients without hypertension or arteriosclerosis (or 15 per cent of the entire group) and seven patients with other cardiovascular disease (or 14.5 per cent) developed other evidence of cardiovascular syphilis. Seventeen of these patients had aortic insufficiency, two had aneurysm, and two had both. No correlation was found to exist between the progression of aortitis and the presence of arteriosclerosis or hypertension, usual type of labor, or adequacy of treatment since the diagnosis of aortitis. In each of these groups the patients whose aortitis progressed compare closely with the general series. It is of interest that only four of these patients had twenty or more treatments with arsenic injections and that four others had no treatment at all previous to the diagnosis of aortitis.

Table VI presents the average ages and periods of observation for the patients in this series who developed other signs of cardiovascular syphilis.

TABLE VI. DATA ON PATIENTS WHO DEVELOPED AORTIC INSUFFICIENCY OR ANEURYSM FOLLOWING THE DIAGNOSIS OF AORTITIS

	NO COMPLICATING CARDIOVASCULAR DISEASE	COMPLICATING CARDIOVASCULAR DISEASE
Total number of patients who developed progressive cardiovascular syphilis other than aortitis	14	7
Number with aortic insufficiency	10	7
Number with aneurysm	2	0
Number with aneurysm and aortic insufficiency	2	0
Average age at diagnosis of aortitis	51.3	54.5
Average number of years from diagnosis of aortitis to diagnosis of other cardiovascular syphilis	3.6	3.5
Average number of years from diagnosis of aortitis to the time of last report	10	9
Number of patients who developed aortic insufficiency or aneurysm dead at last report	1	4

The average age at diagnosis was 51.3 years for those without cardiovascular disease and 54.5 years for the group with complicating arteriosclerosis and hypertension. The average ages for the groups at the last report were 57.6 and 61 years, respectively. One patient without hypertension died at 73 years of age. He had had aortitis for ten years and aortic insufficiency for nine years, and he died in heart failure. Four patients who had hypertension or arteriosclerosis died. Their ages were 51 to 66 years at the time of their deaths. They

had been followed for a total of five to eight years since the diagnosis of aortitis and three to six years following the diagnosis of aortic insufficiency, except for one patient who died during the hospitalization in which the diagnosis of aortic insufficiency was made. They all died in cardiac failure. The diagnosis was confirmed at autopsy in one patient, while another proved to have had rheumatic heart disease.

C. Complicating arteriosclerosis or hypertension: It is necessary to emphasize the fact that patients with hypertension or arteriosclerosis have a poorer prognosis than those without these cardiovascular disorders. This is presumably because the prognosis of either of these diseases is worse than that of aortitis. Those with complicating cardiovascular disease are an older age group (see Table I). There was no increased incidence of aortic insufficiency or aneurysm in these patients.

D. Age: There is a widespread impression that younger patients with cardiovascular syphilis have a bad prognosis. Thirteen of the patients in this series had aortitis diagnosed when they were less than 40 years old. There is no evidence that they died earlier, were followed for a shorter period of time, worked harder, had poorer general health, or were more prone to develop other cardiovascular syphilitic lesions than the group as a whole.

Twenty-five of these patients were 60 years or over at the time of diagnosis. Ten of these had no hypertension at the time of diagnosis. They were followed for an average of six years. Two died, and three developed aortic insufficiency in an average period of three years. Of the fifteen with arteriosclerosis or hypertension, only two developed aortic insufficiency, but nine died.

E. Occupation: The patients are classified according to their usual activity at the time of the diagnosis of aortitis. Ten did strenuous physical labor as their usual occupation, seventy-six did moderately heavy work, and the remaining fifty-one had sedentary occupations. Of those doing hard labor, the average age at diagnosis was 47 years, and they were followed for an average of 5.7 years. Five of them died. One of them developed aortic insufficiency. The group whose usual occupation was sedentary did not differ significantly from the entire series.

F. Change in titer of the serologic test for syphilis following treatment: In this series, the serologic test for syphilis, having been positive, became less positive or negative in fifty-five patients (forty-six of whom had adequate treatment following diagnosis). There was no significant relationship between this change, progression of the cardiovascular syphilis, or mortality.

G. Analysis of deaths: Twenty-two patients with complicating arteriosclerosis or hypertension and twenty-two patients without other cardiovascular disease died. This group as a whole received little treatment, particularly before the diagnosis of aortitis was made. No significant correlation with the type of work is noted.

It was possible to arrive at an idea of the cause of death in most cases from the descriptions on death reports or from the symptoms described by the attend-

ing doctor or relatives. In general, sudden death, heart attack with pain and rapid death, and so forth were considered to indicate probable myocardial infarction. Altogether seven patients fall into this category. Seven more died of "heart failure." In three, the cause of death was obscure, but it appeared to be cardiac or was known to be due to other causes in which cardiac disease appeared to play a significant role. The cause of death was frankly unknown in five patients. In twenty-two patients death was known to be due solely to some other disease. In eight of these (seven of whom had complicating arteriosclerosis or hypertension at the time of the diagnosis of aortitis) the cause of death was a cerebrovascular accident. Of the sixteen patients in whom autopsies were performed, coronary ostial stenosis was observed only twice. Both of these patients had developed aortic insufficiency and suffered "sudden death."

TABLE VII. AN ANALYSIS OF PATIENTS WITH AORTITIS WHO DIED

	NO COMPLICATING CARDIOVASCULAR DISEASE	COMPLICATING CARDIOVASCULAR DISEASE
Total number of patients who died	22	22
Average age at diagnosis of aortitis	53	55
Average number of years followed	4.8	6
Number who developed aortic insufficiency or aneurysm	1	4
Number with hypertension or arteriosclerosis at the time of death	3	22

5. *Treatment.*—The relationship of adequate treatment before and after diagnosis to prognosis was impossible to determine because of the small number of patients in each group. Table VIII presents the number of patients having adequate treatment (considered to be anything over twenty injections of an arsenical preparation or 2.4 million units of penicillin) and those with less or no treatment.

TABLE VIII. PATIENTS RECEIVING TREATMENT IN AORTITIS RELATED TO DEATH RATE

	INADEQUATE TREATMENT BEFORE DIAGNOSIS OF AORTITIS		ADEQUATE TREATMENT BEFORE DIAGNOSIS OF AORTITIS	
	INADEQUATE TREATMENT AFTER DIAGNOSIS OF AORTITIS	ADEQUATE TREATMENT AFTER DIAGNOSIS OF AORTITIS	INADEQUATE TREATMENT AFTER DIAGNOSIS OF AORTITIS	ADEQUATE TREATMENT AFTER DIAGNOSIS OF AORTITIS
Total number of patients	36	27	54	24
Number patients dead at last report	18	9	14	3
Per cent of total dead	50	33	26	12.5

There was a lower death rate in the adequately treated group. However, because of the dissimilarity of the treatment groups, no conclusions regarding

the efficacy were warranted, and further analysis of the material did not give consistent results. Of the thirty-six patients who did not receive adequate treatment at any time, only one developed aortic insufficiency or aneurvsm.

SUMMARY

1. One hundred forty-one patients with syphilitic aortitis diagnosed clinically at the New York Hospital between 1935 and 1950 were studied.

2. All patients with aortic insufficiency, aneurysm, or coronary ostial stenosis due to syphilis at the time of diagnosis were excluded.

3. Patients who had arteriosclerosis or hypertension at the time of diagnosis were included in the study.

4. The average age at diagnosis was 51 years. White men predominated (63 per cent), white women being the next most common (20 per cent); Negro men were more common than Negro women.

5. The subsequent history of the patients substantiated the diagnosis thirty-nine times by the development of other evidence of aortic syphilis, positive angiocardiographic diagnosis, or autopsy findings. Seven times the diagnosis was apparently in error as indicated by lack of confirmation by angiocardiogram or autopsy.

6. The diagnosis was most often made in the presence of x-ray evidence of aortic dilatation (present in 122 patients), accentuation of the aortic second sound (found sixty-eight times), submanubrial dullness (found fifty-two times), or an aortic systolic murmur (present in seventy-eight patients). The diagnosis was made in the presence of any one or any combination of these changes. Electrocardiogram, symptoms, pulse pressure changes, and heart size were not useful in making the diagnosis. The single sign or symptom considered most important in making the diagnosis was x-ray evidence of aortic dilatation in eighty-three patients and accentuated second aortic sound in thirty-seven patients.

7. A positive angiocardiographic diagnosis appears to be significant, whereas a normal angiocardiogram does not rule out aortitis.

8. Fifteen per cent of all patients in this series, whether or not they had hypertension or arteriosclerosis, developed aortic insufficiency or aneurysm after an average of 3.5 years. Their prognosis was no worse than that of the group as a whole.

9. No worse prognosis was found to exist in those patients in whom the diagnosis was made at an early age than in the group as a whole.

10. The prognosis was not affected by the age of the patient at the time of the diagnosis of aortitis.

11. The prognosis of those patients who had arteriosclerosis and hypertension at the time of the original diagnosis of aortitis was worse than the group as a whole and is apparently that of the hypertension and arteriosclerotic heart disease.

12. The patients in this series were followed for an average of 7.1 years. Sixty-two per cent were followed for more than five years and 41 per cent for over ten years. The death rate was no greater in the group followed ten years and more (12 per cent) than for the other groups.

CONCLUSIONS

1. The diagnosis of uncomplicated syphilitic aortitis can be made clinically with reasonable accuracy. The presence of hypertension and arteriosclerosis does not make the diagnosis of syphilitic aortitis significantly more hazardous.

2. A relatively low death rate in a group of elderly patients followed for a long time period and a low incidence of the development of aortic insufficiency or aneurysm suggest that uncomplicated syphilitic aortitis carries a favorable prognosis.

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THE CARDIAC COMPLICATIONS OF HEMOCHROMATOSIS

Report of a Case Including Radioiron Studies and a Note on Etiology

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A CASE of hemochromatosis with heart failure in a young, adult woman has been studied, and the results of clinical and radioiron investigations are presented. The radioiron studies corroborate our findings in a previous case[1] and offer a possible explanation of the mechanism underlying the cardiac failure.

The disease is uncommon in women (16 out of 311 cases)[2] and is usually seen in an older age group of 50 to 55 years. Cardiac complications are rare, in spite of the heavy deposits of iron which may be present in the heart muscle.[2,3]

CASE REPORT

First Admission.—The patient was admitted to the Johannesburg General Hospital on Feb. 6, 1950, complaining of amenorrhea for twenty months. Previous health had been good, and she had given birth to a normal baby in 1946. Six months after the onset of the amenorrhea, the skin began to darken. Both family and systemic histories were noncontributory.

Physical examination: She was well developed. A generalized, slaty gray skin pigmentation was found, and both axillary and pubic hair were scanty. A bigeminal rhythm accounted for a pulse rate of 44 per minute, which was one-half the rate counted over the heart. The blood pressure was 126/70 mm. Hg, and there was no clinical cardiomegaly or abnormality of the heart sounds. The liver edge was just palpable, being firm and nontender. Gynecological examination proved negative.

Progress: She was asymptomatic in the hospital. She had frequent extrasystoles, but these caused no subjective disability. The patient was discharged, with no definite diagnosis, on Feb. 27, 1950.

Laboratory data: A complete blood count showed the following: hemoglobin, 13.8 Gm. per cent; erythrocytes (per cubic millimeter), 4,650,000; leukocytes (per cubic millimeter), 10,000; neutrophils, 41.0 per cent; monocytes, 11.0 per cent; lymphocytes, 44.5 per cent; eosinophils, 3.5 per cent; basophils, 0 per cent. In a blood protein determination albumin was 2.5 mg. per cent, globulin 3.9 mg. per cent. Serum sodium was 344 mg. per cent; serum sodium chloride, 560 mg. per cent; blood urea nitrogen, 38 mg. per cent. The sugar tolerance curve (after 50 Gm. of glucose by mouth) was as follows: fasting level, 100 mg. per cent; 15 minutes, 105 mg. per cent; 30 minutes, 110 mg. per cent; 60 minutes, 150 mg. per cent; 120 minutes, 120 mg. per cent; 180 minutes, 105 mg. per cent. The results of liver function tests were: thymol turbidity test, 3.5 units; thymol flocculation, negative; cephalin cholesterol flocculation (twenty-four hour reading), +++ positive; Takata-Ara (Ucko's modification), ± positive. The prothrombin index was 83 per cent. A modified Ide test for syphilis was negative. Urinalysis was normal. A Kepler-Robinson-Power test was positive (25). A skin biopsy was negative.

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CONCLUSIONS

1. The diagnosis of uncomplicated syphilitic aortitis can be made clinically with reasonable accuracy. The presence of hypertension and arteriosclerosis does not make the diagnosis of syphilitic aortitis significantly more hazardous.

2. A relatively low death rate in a group of elderly patients followed for a long time period and a low incidence of the development of aortic insufficiency or aneurysm suggest that uncomplicated syphilitic aortitis carries a favorable prognosis.

The authors wish to express their indebtedness to Dr. William A. Brumfield for his helpful suggestions regarding the statistical presentations in this paper.

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THE CARDIAC COMPLICATIONS OF HEMOCHROMATOSIS

Report of a Case Including Radioiron Studies and a Note on Etiology

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A CASE of hemochromatosis with heart failure in a young, adult woman has been studied, and the results of clinical and radioiron investigations are presented. The radioiron studies corroborate our findings in a previous case[1] and offer a possible explanation of the mechanism underlying the cardiac failure.

The disease is uncommon in women (16 out of 311 cases)[2] and is usually seen in an older age group of 50 to 55 years. Cardiac complications are rare, in spite of the heavy deposits of iron which may be present in the heart muscle.[2,3]

CASE REPORT

First Admission.—The patient was admitted to the Johannesburg General Hospital on Feb. 6, 1950, complaining of amenorrhea for twenty months. Previous health had been good, and she had given birth to a normal baby in 1946. Six months after the onset of the amenorrhea, the skin began to darken. Both family and systemic histories were noncontributory.

Physical examination: She was well developed. A generalized, slaty gray skin pigmentation was found, and both axillary and pubic hair were scanty. A bigeminal rhythm accounted for a pulse rate of 44 per minute, which was one-half the rate counted over the heart. The blood pressure was 126/70 mm. Hg, and there was no clinical cardiomegaly or abnormality of the heart sounds. The liver edge was just palpable, being firm and nontender. Gynecological examination proved negative.

Progress: She was asymptomatic in the hospital. She had frequent extrasystoles, but these caused no subjective disability. The patient was discharged, with no definite diagnosis, on Feb. 27, 1950.

Laboratory data: A complete blood count showed the following: hemoglobin, 13.8 Gm. per cent; erythrocytes (per cubic millimeter), 4,650,000; leukocytes (per cubic millimeter), 10,000; neutrophils, 41.0 per cent; monocytes, 11.0 per cent; lymphocytes, 44.5 per cent; eosinophils, 3.5 per cent; basophils, 0 per cent. In a blood protein determination albumin was 2.5 mg. per cent, globulin 3.9 mg. per cent. Serum sodium was 344 mg. per cent; serum sodium chloride, 560 mg. per cent; blood urea nitrogen, 38 mg. per cent. The sugar tolerance curve (after 50 Gm. of glucose by mouth) was as follows: fasting level, 100 mg. per cent; 15 minutes, 105 mg. per cent; 30 minutes, 110 mg. per cent; 60 minutes, 150 mg. per cent; 120 minutes, 120 mg. per cent; 180 minutes, 105 mg. per cent. The results of liver function tests were: thymol turbidity test, 3.5 units; thymol flocculation, negative; cephalin cholesterol flocculation (twenty-four hour reading), +++ positive; Takata-Ara (Ucko's modification), ± positive. The prothrombin index was 83 per cent. A modified Ide test for syphilis was negative. Urinalysis was normal. A Kepler-Robinson-Power test was positive (25). A skin biopsy was negative.

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An electrocardiogram on Feb. 8, 1950, showed inconstant bigeminal rhythm due to alternating ventricular extrasystoles. The rate was 80 per minute. Basic rhythm showed a flat T wave in Lead V_6 and diphasic (+ —) T waves in V_4 and V_5 (Fig. 1). There were runs of ventricular extrasystoles up to six beats. On Feb. 21, 1950, the inconstant bigeminal rhythm was still present.

Roentgenograms of the heart, lungs, and skeleton were normal.

Second Admission.—The patient had been well until four days before readmission on March 28, 1951, when she developed short bouts of "palpitations" with a rapid, regular heart rate. During one such attack, she became extremely breathless and lost consciousness for a few moments.

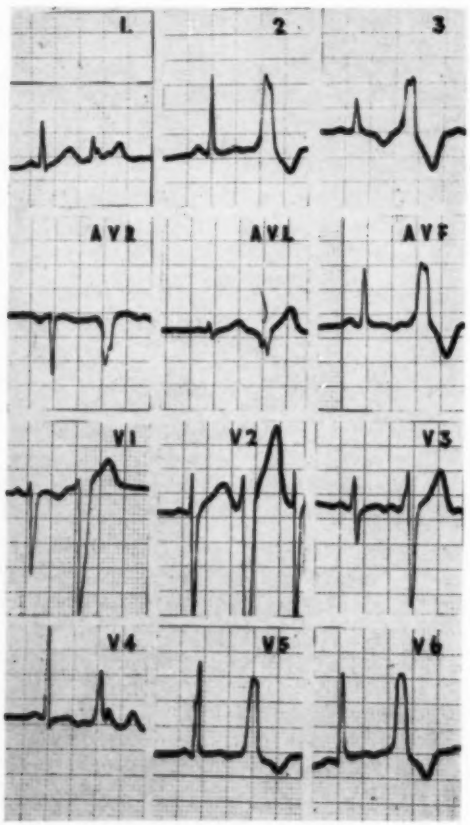

Fig. 1.—Electrocardiogram taken on Feb. 8, 1950. Bigeminal rhythm is due to ventricular extrasystoles. The basic rhythm shows a flat T wave in Lead V_6 and diphasic (+ —) T waves in V_4 and V_5.

Physical examination: There were generalized skin pigmentation and marked orthopnea. The pulse rate was ± 170 per minute, the rhythm was irregular, and the blood pressure was 80/55 mm. Hg. She was in congestive cardiac failure and peripheral circulatory failure with a cold and clammy skin. The neck veins were engorged and pulsatile at an angle of 45 degrees. The heart was not clinically enlarged, and the sounds were normal. The liver was enlarged 3 fingerbreadths, and the edge was smooth and tender. There was no peripheral edema.

Progress: Digoxin, 0.5 mg., was injected intravenously, and the condition improved dramatically. After two hours, the pulse was regular with a rate of 96 per minute, and the blood pressure rose to 110/65 mm. Hg. Maintenance therapy was continued with 0.25 mg. of digoxin twice daily and with 6 gr. of quinidine sulfate four times daily. After several days there were no signs of congestive failure, and the heart was regular except for occasional extrasystoles. While the patient was in the hospital, the diagnosis of hemochromatosis was established by liver biopsy. She was discharged on April 21, 1951.

Laboratory data: A complete blood count showed the following: hemoglobin, 15.7 Gm. per cent; erythrocytes (per cubic millimeter), 5,000,000; leukocytes (per cubic millimeter), 8,900; neutrophils, 46.0 per cent; monocytes, 7.0 per cent; lymphocytes, 44.5 per cent; eosinophils, 0.5 per cent; basophils, 2.0 per cent. In a blood protein determination albumin was 3.8 mg. per cent, globulin 3.9 mg. per cent. Serum sodium was 337 mg. per cent; serum sodium chloride, 550 mg. per cent; serum potassium, 20 mg. per cent; phosphorus, 4.8 mg. per cent; calcium, 10.6 mg. per cent; cholesterol, 195 mg. per cent; amylase, 74 units. The sugar tolerance curve (after 50 Gm. of glucose by mouth) was as follows: fasting level, 70 mg. per cent; 30 minutes, 78 mg. per cent; 60 minutes, 110 mg. per cent; 90 minutes, 70 mg. per cent; 180 minutes, 60 mg. per cent. The results of liver function tests were: thymol turbidity test, ++ positive; cephalin cholesterol flocculation, negative; Takata-Ara (Ucko's modification), negative; van den Bergh reaction, negative; bilirubin: direct, less than 0.5 mg. per cent, total, less than 0.5 mg. per cent. The icteric index was 10, the prothrombin index 78 per cent. A modified Ide test for syphilis was negative. Urinalysis was normal both chemically and microscopically. There were no excess porphyrins; diastase, 6 Wohlgemuth units, 17-ketosteroids, 8 mg. per cent. A Rous' test was positive. Examination of the feces (twenty-four hour specimen) showed 82 per cent water. Of the solids 12 per cent was fat, 35 per cent of which was unsplit. A roentgenogram of the chest (April 7, 1951) showed a normal heart outline. The basal metabolic rate was +6 per cent.

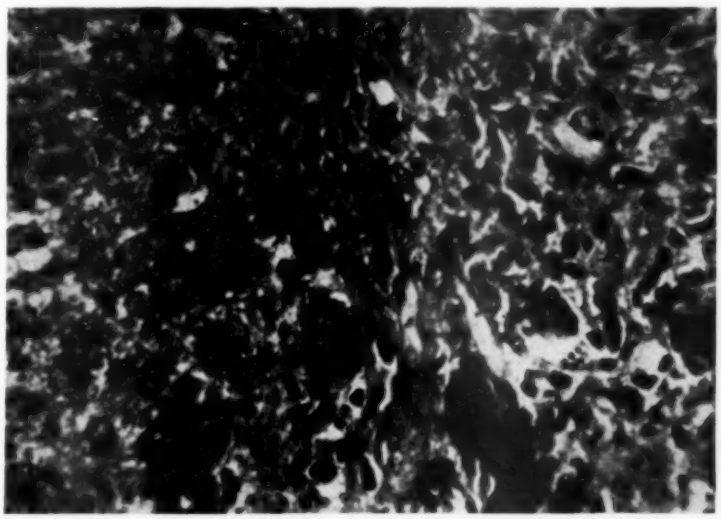

Fig. 2.—Section of liver stained with Prussian blue (magnification ×500) showing heavy iron deposition with moderate portal fibrosis.

Electrocardiograms on March 28, 1951, showed a variable supraventricular (probably nodal) tachycardia, together with numerous ventricular extrasystoles. The rate was 170 per minute. Within half an hour of administering 0.5 mg. of digoxin intravenously, the rhythm became regular, the rate 200 per minute. During the next hour, the rate slowed to 100 per minute. Regular sinus rhythm was present. Between March 30, 1951, and April 5, 1951, while the patient was on digitalis therapy, a sinus rhythm persisted with slow rate. T waves in Leads II and V_6 became flattened, and the R-ST segment showed digitalis effect.

A skin biopsy was normal. A liver biopsy (carried out on April 12, 1951, after a short course of vitamin K therapy) showed the histological features of hemochromatosis, with heavy iron deposition and a moderate portal fibrosis (Fig. 2).

Third Admission.—The patient remained in good health on quinidine sulfate, 6 gr. four times daily, until May 21, 1951, when she developed bouts of extreme paroxysmal breathlessness accompanied by "palpitations" and was readmitted to the hospital in congestive cardiac failure.

Physical examination: The pulse rate was 135 per minute, the rhythm was regular, and the blood pressure was 120/70 mm. Hg. The heart was not clinically enlarged. On auscultation there was a gallop rhythm.

An electrocardiogram showed a sinus tachycardia with a rate of 140 per minute. There was R-ST depression in Leads II, V_5, and V_6 (1½ mm. in the latter). T waves were inverted in II, III, aV_F, and V_6 (patient not on digitalis) (Fig. 3).

Progress: She was treated with bed rest, digoxin by mouth, a salt-free diet, and mercurial diuretics. Response was satisfactory, and she was ready for discharge on June 4, 1951.

At the time of writing (August, 1951) she is able to carry on with her work as a factory machinist. The heart rhythm on maintenance quinidine and digitalis therapy is normal.

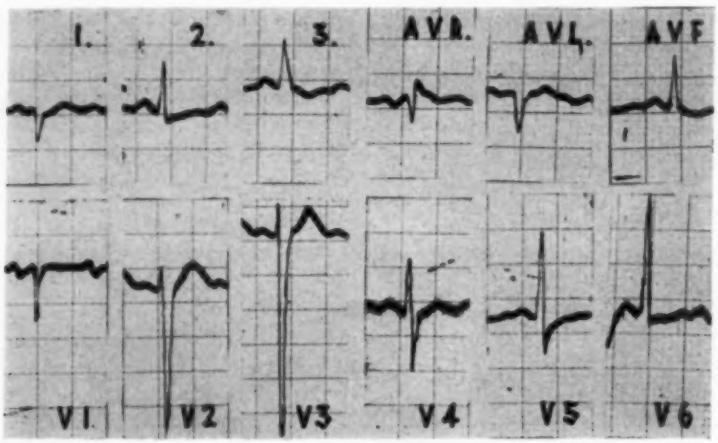

Fig. 3.—Electrocardiogram taken on May 21, 1951. It shows sinus rhythm with flat T waves in Leads II, aV_F, and V_5.

SUMMARY OF RADIOIRON STUDY

Between the second and third hospital admissions, radioiron absorption studies were carried out on this patient. The results are recorded below.

Material and Methods.—Twenty mg. of a mixture of Fe^{55} and Fe^{59} in the form of ferrous sulfate were given to the patient, with an activity of approximately 20 microcuries, measured as Fe^{59}. The dose was given four hours after breakfast, and no attempt was made to modify the normal ward diet prior to the experiment.

The course of the iron was then followed by (1) assays of radioiron in total feces for seven days after administration, (2) measurements of radioiron in blood samples taken at intervals up to fifty days after administration of the ferrous sulfate, and (3) serial in vivo measurements over body organs, up to 100 days.

Control: The results in an adult menopausal control subject with mild diabetes have been included. She was given the same dose of radioiron as the patient and was subjected to the same conditions and measurements. The findings in this case agree with our results in several normal subjects.[9]

Cadaver measurements: In order to establish whether counts obtained over other organs were due to a real deposition of radioiron or to "scatter" from the high radioiron deposition which was found in the liver, a model liver made of "printer's roller composition" was placed in a cadaver of similar body build to

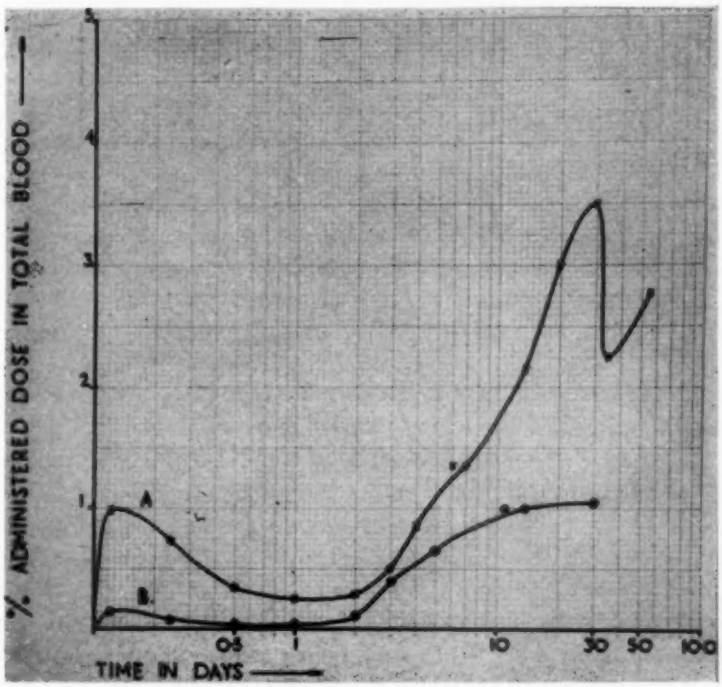

Fig. 4.—Graphic representation of the percentage of the administered dose of radic iron in the total blood. *A* = patient; *B* = control.

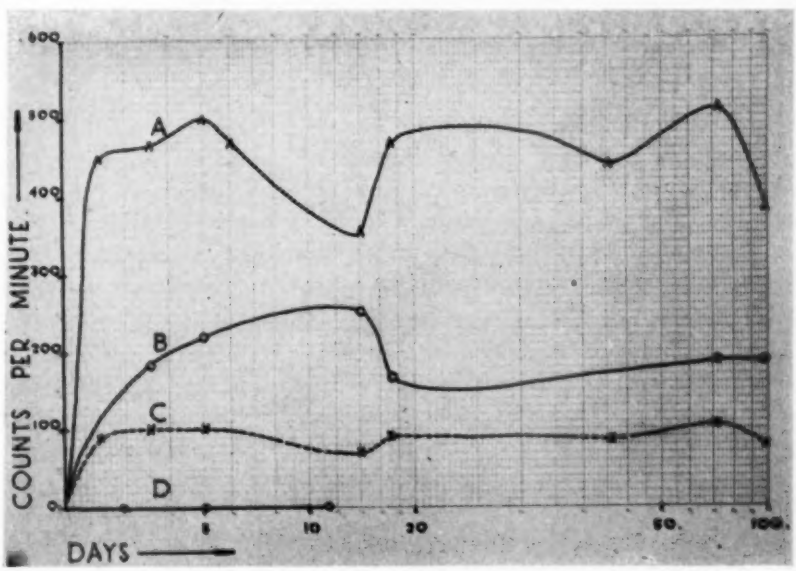

Fig. 5.—Graph showing in vivo counts obtained over mid-heart and mid-liver in patient and control. *A* = counts over mid-liver in patient; *B* = counts over mid-heart in patient; *C* = predicted curve to be expected over mid-heart of patient, due to radiation "scatter" from liver; *D*= counts over mid-heart and mid-liver of control.

the patient. Multiple measurements were then taken, including those from the sites used in our in vivo experiments.

The full techniques of the methods used in our radioiron assays are similar to those which have already been reported.[1]

Results.—

1. Feces excretion for first seven days after administration: The patient's excretion was 5.71 microcuries, i.e., ± 28 per cent of the administered dose. Execretion of the control subject was 14.44 microcuries, i.e., ± 74 per cent of the administered dose.

2. Blood uptake: This is represented graphically using a logarithmic time scale (Fig. 4) and is given as the percentage of the administered dose in the total blood volume. The initial peak in the first twenty-four hours probably represents the plasma uptake. The subsequent drop is presumably due to the storage of radioiron. This is followed by the gradual rise, due to the liberation of this iron for hemoglobin formation. After thirty days this reached a peak of 3.5 per cent in the patient as compared with 1.1 per cent in the control.

3. In vivo measurements: Measurements over the mid-heart and mid-liver have been represented graphically (Fig. 5). In addition, a curve is included to represent the counts to be expected over the mid-heart due to "scatter" from the radioiron in the liver. The graph demonstrates three points: (a) There was a very high uptake of radioiron in the liver of the control. (b) Readings over the mid-heart of the patient gave readings higher than could be accounted for by radiation "scatter." They seem to represent a real deposition of radioiron in the heart muscle. (c) No readings above background were obtained over the liver or any other organ of the control.

DISCUSSION

The salient findings in this case were myocardial failure, amenorrhea, skin pigmentation, and enlargement of the liver, occurring in a young, adult woman suffering from hemochromatosis.

The association of this disease with heart failure has been reported in only thirty-three cases.[4] Twenty-two of these were similar to the present one, in that they showed evidence of sexual hypoplasia or regression, together with enlargement of the liver and heart failure. However, only two women have previously been reported with such a clinical presentation.[5,6] Both were young (34 years and 18 years, respectively), and in both amenorrhea was the initial symptom. Skin pigmentation and hepatic enlargement were present, but sugar tolerance was normal.

Involvement of the heart in hemochromatosis is commonly associated with arrhythmias and electrocardiographic abnormalities of a nonspecific nature.[3,4] Congestive cardiac failure is the usual cause of death, and the response to medical treatment is uniformly poor. The average period of survival after the onset of cardiac symptoms is less than a year. The average age at death in this group is 38 years, as compared with an average age of onset of between 45 and 50 years in those patients without clinical evidence of heart involvement.

The cause of the heart failure in hemochromatosis is not known. Postmortem examinations have shown varying degrees of deposition in the heart muscle of patients with and without heart failure. Sheldon,[2] in his monograph, wrote: "Several cases have died from cardiac failure but, on the whole, the extensive deposits of iron laid down in this organ produce little clinical evidence of their presence." The complete lack of correlation between the extent of iron deposition in the myocardium and the presence of heart failure has led several French authors to invoke endocrine factors to explain the cardiac failure.[7,8]

The results of radioiron studies in this case and in a young male subject with hemochromatosis and cardiac involvement previously reported by us[1] seem to offer another explanation of the heart failure. Clinically, the two cases were very similar. The patients were in their early twenties, had evidence of sexual hypoplasia, and showed advanced myocardial damage with bouts of paroxysmal arrhythmia. Their uptake after a standard oral dose of radioiron was compared with the uptake in four older subjects suffering from hemochromatosis, but with no clinical evidence of myocardial damage. The percentage of the administered dose retained in the body and the levels of the blood and liver uptakes were far higher in these two patients although the other four subjects all had uptakes greater than normal.[9] These results seem to indicate that young subjects with hemochromatosis absorb greater quantities of iron from the gut than do older subjects.

The much higher incidence of heart failure in the younger age group may possibly be related to the fact that the disease is present in a more acute form in which iron is being absorbed and deposited at a much accelerated rate. On this basis, the damage to the myocardium would not be related so much to the *degree* of iron deposition as to the *rate* at which it is being laid down. It would thus be possible to explain why patients with heavy iron deposition in the cardiac muscle have shown no clinical signs of myocardial damage, while others with less iron deposition have had extreme and irreversible heart failure.

SUMMARY

A case of hemochromatosis in a young, adult woman is presented, the salient clinical findings being heart failure, skin pigmentation, amenorrhea, and enlargement of the liver. Only two similar cases in women have been described.

The results of radioiron absorption studies show that 75 per cent of a total oral dose of 20 mg. of ferrous sulfate was retained in the body. The level of radioiron in the blood reached a maximum of 3.5 per cent of the administered dose after a period of thirty days, and in vivo counts showed a large deposition of radioiron in the liver. Counts over the heart seemed to indicate a real deposition in this organ.

It is suggested that heart failure in hemochromatosis is related more to the rate at which iron is laid down in the cardiac muscle than to the absolute quantity deposited.

Grateful thanks are due to Professor G. A. Elliott for permission to publish this case study and for his unfailing guidance and encouragement. We have also had the helpful advice of Professor J. Gillman and Dr. T. Gillman. Thanks are also due to Dr. C. B. Ellis, Dr. D. V. Dawber, Dr. R. I. H. Welsh, A. M. Shevitz, and S. Dry for invaluable technical assistance.

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THE EFFECT OF MYXEDEMA ON THE CARDIOVASCULAR SYSTEM

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THE effect of myxedema on the heart and circulation has been the subject of numerous studies since Zondek[1] first described "myxedema heart" and Fahr[2] reported the occurrence of heart failure in this disease. Although the causation of congestive failure by myxedema has been questioned, there is general agreement that certain objective changes in the cardiovascular system may develop which diminish or disappear when thyroid treatment is established. The clinical features of this condition, as cited by Mussio Fournier,[3] are "difficulty in perceiving the apex beat; muffling of the cardiac tones; tendency to bradycardia; slight to great increases in the size of the heart; enlargement of the vascular pedicle of the heart; decreased amplitude of cardiac contractions." Electrocardiographic changes, consisting of decrease in amplitude of all complexes, but especially of the P and T waves, have been repeatedly observed. Hallock[4] gave a complete review of the literature to 1933, and reports made since his publication have for the most part confirmed the earlier clinical findings.

Case reports of the occurrence of pericardial effusion as well as other serous effusions in myxedema have been made by numerous authors. Recently, Kern, Soloff, Snape, and Bello[5] have emphasized the frequency of pericardial effusion as an early manifestation and have suggested that such effusion will explain many of the clinical findings referable to the heart as well as the electrocardiographic changes.

The situation in regard to the relationship between the myxedema and heart disease is complicated by the fact that the incidence of atherosclerosis in these persons is high,[6] and this may be related to the elevation of serum cholesterol, which commonly occurs in this disease.[7,8]

Coronary insufficiency, as manifested by the development of angina pectoris of effort or of acute myocardial infarction, is a not uncommon event when the basal metabolic rate, and hence the demand on the heart, is increased in patients with myxedema by thyroid medication. Rarely, the reverse occurs, and angina, present during the myxedematous stage, is relieved under thyroid therapy. According to Mussio Fournier, there have been six such cases published, including the original report by himself and associates.[9]

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Numerous physiological studies of the circulation in myxedema have been made. The cardiac output has been found to be decreased,[10-13] the circulation time prolonged,[10,12,14-16] and the circulating plasma and total blood volumes diminished.[16,17] The prolongation of the circulation time and the decrease in cardiac output are said to parallel in a rough way the reduction of basal metabolic rate, although the circulation time is not always prolonged[12] and the cardiac output may be reduced to a greater extent than the decrease in oxygen consumption,[12] thus resulting in an increased arteriovenous oxygen difference. For the most part, the reports of circulatory measurements that have been made dealt mainly with one or two aspects of the circulation, and many of them have been made by indirect methods, particularly most of the estimations of cardiac output.

The only study of cardiac output by the method of cardiac catheterization of which we are aware is one recently reported by Scheinberg, Stead, Brannon, and Warren.[11]

The present report is a study of the physiology of the circulation in five patients with myxedema, including observations during exercise in two and studies made after medication with thyroid extract in two.

METHODS

The techniques of the methods employed have been described in detail elsewhere.[18] The cardiac outputs were estimated by the direct Fick method, mixed venous blood being obtained from the pulmonary artery or the right ventricle, and direct measurement of the arterial oxygen content was made in all instances except in Patient 1 in whom it was estimated as 95 per cent of the oxygen capacity. Oxygen consumption was determined by the Benedict-Roth method in all cases, except in Patients 1 and 2, in whom, both at rest and during exercise, the oxygen consumption was determined by the analysis of expired air collected in a Tissot gasometer, the analysis being carried out by the Haldane method. The exercise was performed in the supine position and consisted of pushing with one foot against a pedal weighted with 25 pounds, raising the weight about a foot, at a rate of approximately thirty times a minute. The duration of the exercise was two to three minutes, and expired air was collected over the entire period after the first fifteen seconds of exercise. Mixed venous blood samples were collected at the end of one to two minutes of exercise, and the values for oxygen content, which were in close agreement, were averaged. Pressure curves were registered immediately before the beginning and just before and after the cessation of exercise. Intracardiac pressures were recorded by optical registration with Hamilton manometers, and femoral arterial pressures were directly recorded by the same technique, except in Patient 1 and at the time of the second study of Patient 3, in whom brachial arterial pressures were measured indirectly by a mercury sphygmomanometer. The zero reference point for peripheral venous and intracardiac pressure measurements was taken as 5 cm. below the angle of Louis. Plasma volumes were estimated by the method of Gregersen with Evans blue, using an Evelyn colorimeter, with control and single ten-minute samples.[19] The total circulating blood volume was calculated from the plasma volume and the hematocrit.

OBSERVATIONS

PATIENT 1.—A 21-year-old, single, white clerk was admitted to the hospital with the complaint of shortness of breath. Two weeks before admission, she developed a cough and felt feverish and shortly thereafter became short of breath. One week later, the dyspnea became much worse, and she was so orthopneic that she slept in a chair. For one day she had had some edema of the ankles. She had been obese since childhood, rather slow mentally and physically, and sensitive to cold, and the skin had been pale and dry. Five years previously, she had been given medication (? thyroid) for the obesity and "low blood pressure," and on this she lost 35 pounds and felt much better, but she stopped the treatment after a few months. The menses were normal.

On physical examination, she was a pale, obese, puffy-faced girl, mildly orthopneic and coughing. The skin and hair were dry and coarse, and the tongue was slightly large. There was no obvious venous distention. The lungs were negative to examination, except for many medium crackling râles at each base. The heart was enlarged, the rhythm was regular at a rate of 80, and the sounds were of good quality with no murmurs. The blood pressure was 100 mm. Hg systolic and 70 mm. Hg diastolic. The liver was not palpable, and there was slight pitting edema of the ankles. The remainder of the examination was normal.

Laboratory studies before treatment were as follows: The urine was repeatedly normal. The hemoglobin was 11.0 Gm.; red blood cell count, 3.23 million; white blood cell count, 9,000; hematocrit, 36 per cent. Blood smear revealed normal red and white cells. The icteric index was 5. Blood Hinton reaction was negative. The blood nonprotein nitrogen was 36 mg. per cent; serum cholesterol, 226, 232, and 230 mg. per cent; venous pressure on admission, 140 mm. of water; insulin tolerance test (0.05 unit per kilogram of body weight intravenously): fasting blood sugar, 60 mg. per cent; 30 minutes, 55 mg. per cent; 48 minutes, 70 mg. per cent; 120 minutes, 70 mg. per cent. Roentgenograms of the chest on admission showed slight congestive changes at the lung bases and an enlarged heart. Other tests are shown on Table I.

Course.—On admission the temperature was 100.8° F. by rectum, but within twelve hours it dropped to normal and remained at that level. The patient was treated by bed rest, a salt-free diet, and penicillin. Her subjective condition remained essentially unchanged, although the râles in the chest diminished and the edema cleared. Evidence for continuing infection in the chest or elsewhere was not present, as judged by the clinical state, lack of fever, leukocytosis, or positive x-ray findings of pneumonia. Twelve days later, three days after the special cardiac studies were made, she was started on thyroid extract (U.S.P.) 0.065 Gm. daily. Within a week she was improved; she was discharged after fifteen days of thyroid medication at which time the thyroid was increased to 0.1 Gm. daily. She was followed in the outpatient department and reported steady improvement, being more alert and more active physically and losing 5 pounds. The second series of cardiac studies was made eight weeks after the onset of therapy.

At the time the initial physiological studies were made, after the patient had been eight days in the hospital, she was still somewhat orthopneic, and there were a few râles at the lung bases, but the peripheral congestive phenomena had cleared. Because of the lack of evidence for any other etiological cause for heart disease, such as acute rheumatic or nonspecific myocarditis and arteriosclerosis, and the rapid improvement after thyroid medication was commenced, the responsibility of the myxedema in producing the circulatory changes is clear. Further evidence for this is afforded by the typical cardiac silhouette by roentgenogram and the electrocardiographic pattern (Fig. 1), with prompt return of both to normal under treatment. The finding of a cholesterol level which was only questionably elevated is not inconsistent with myxedema, since normal values were found in several of the forty-seven patients with induced myxedema reported by Gilligan and associates[8]; Peters and Man[10] pointed out the limited value of this procedure. After treatment for six weeks, the cholesterol level in this patient had fallen slightly to 198 mg. per cent.

Against a diagnosis of hypopituitarism without hypothyroidism are the normal menstrual history, the normal insulin tolerance curve, and the improvement after therapy not only in the circulatory symptoms, but in the chronic symptoms of hypometabolism as well.

The special studies of the circulation revealed that the cardiac output was diminished out of proportion to the lowering of the oxygen consumption, as

TABLE I. CIRCULATORY MEASUREMENTS

PATIENT	BASAL METABOLIC RATE	OXYGEN CONSUMPTION (C.C. PER MINUTE)	HEART RATE	CARDIAC OUTPUT (L. PER MINUTE)	CARDIAC INDEX (L. PER MINUTE PER SQ. M.)	STROKE OUTPUT (C.C. PER BEAT)	ARTERIOVENOUS OXYGEN DIFFERENCE (C.C. PER LITER)	FEMORAL ARTERY PRESSURE (MM. Hg)			PULMONARY ARTERY PRESSURE (MM. Hg)		
								SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC	MEAN
1	−28												
	−17												
	−25												
	−30*	173	70	2.5	1.2	36	69	104	84	94			7
	−2												
	−16*	209	64	7.0	3.5	110	30	115	70				
2	−27												
	−30												
	−33												
	−26*	169	47	2.7	1.5	57	60	84	42	62	27	10	16
3	−14												
	−23												
	−28												
	−34												
	−2*	195	62	3.8	2.2	61	51	169	93	120	18	9	11
	+4*	218	55	4.4	2.6	80	49	174	104		20	9	14
4	−55												
	−43												
	−38*	108	68	3.0	2.1	44	36	152	70	102	20	9	16
5	−33												
	−22*	144	84	3.6	2.2	43	40	133	76	98	13	6	9
Normal					3.3[1,2]		45[1,2,3]				25[3]	8[3]	15[3]

*Metabolic rate determined during cardiac catheterization.
†Calculated from estimated mean of diastolic plus one-half pulse pressure in the brachial artery.
‡Calculated from estimated mean pulmonary arterial pressure of 10 mm.
[1]Average normal values as cited by Stead and associates.[27]
[2]Average normal values as cited by Cournand and associates.[25]
[3]Average normal values as cited by McMichael and Sharpey-Schafer.[26]

shown by the increased peripheral utilization of oxygen with an arteriovenous oxygen difference of 69 c.c. per liter of normal flow. When the patient was exercised for 2 minutes, with an increase in the oxygen consumption from 173 to 283 c.c. per minute, the cardiac output increased from 2.5 to 3.9 L. per minute, which is within the normal range of increase. Neither the mean pulmonary arterial, right auricular, or peripheral venous pressure was elevated at rest or changed with exercise, and the two latter pressures were unaffected when manual pressure was exerted over the right upper quadrant.

The circulation time as measured from the arm to tongue by magnesium sulfate was 15 and 18 seconds on two occasions in spite of the diminished cardiac

IN FIVE PATIENTS WITH MYXEDEMA

RIGHT VENTRICLE PRESSURE (MM. Hg)		RIGHT AURICULAR PRESSURE (MM. Hg)	PERIPHERAL VENOUS PRESSURE (MM. Hg)	SYSTEMIC PERIPHERAL RESISTANCE (DYNES SECONDS CM.$^{-5}$)	TOTAL PULMONARY RESISTANCE (DYNES SECONDS CM.$^{-5}$)	BLOOD VOLUME				
SYSTOLIC	DIASTOLIC					PLASMA VOLUME (C.C.)	C.C.	DEVIATION FROM PREDICTED NORMAL[4]	HEMATOCRIT	CIRCULATION TIME (ARM-TONGUE) (SECONDS)
15	1	0	2	3000†	222	2377	3660	−17	35	15, 18
18	3			1050†	115‡	3025	4660	+ 3	35	18
28	2			1835	651	3847	5481	0	30	40, 27 23
19 22	3 −2	−1 −2	4 2	2825 2520	226 252					
		5	5	2671	456	1850	2720	−30	32	
		1	−2	2190	166	2375	3345	−18	29	16
25[6]	2[5]	3[7]	6[7]	1200[1,2]	200[6]				40–45	13[8]

[4]Average normal values as cited by Gibson and Evans.[29]
[5]Average normal values as cited by Cournand.[28]
[6]Average normal values as calculated from data given by Cournand.[28]
[7]Average normal values as cited by Richards and co-workers.[30]
[8]Average normal values as cited by Bernstein and Simkins.[31]

output. The plasma volume was within the normal range, but because of the low hematocrit, the total blood volume was reduced.

The patient was again studied two months after starting therapy with 0.1 Gm. of thyroid extract daily. Although she had lost but 5 pounds in weight, the symptoms had entirely disappeared, and both subjectively and objectively she was brighter, more alert, and more active. The basal metabolic rate two days before the cardiodynamic observations were made was recorded in the clinic as −2 per cent, although at the time of our study it was −16 per cent. All studies of the circulation made at this follow-up visit were normal, both at rest and during exercise. The plasma and blood volumes had increased, although the hematocrit was unchanged. The circulation time was still 18 seconds.

TABLE II. EFFECT OF EXERCISE ON CIRCULATORY DYNAMICS OF TWO PATIENTS WITH MYXEDEMA

PATIENT		HEART RATE	OXYGEN CONSUMPTION (C.C. PER MINUTE)	CARDIAC OUTPUT (L. PER MINUTE)	STROKE VOLUME (C.C.)	ARTERIOVENOUS OXYGEN DIFFERENCE (C.C. PER LITER)	FEMORAL ARTERY PRESSURE (MM. Hg)			PULMONARY ARTERY PRESSURE (MM. Hg)			RIGHT VENTRICLE PRESSURE (MM. Hg)		RIGHT AURICULAR PRESSURE (MM. Hg)	PERIPHERAL VENOUS PRESSURE (MM. Hg)
							SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC		
1	Before medication															
	Rest	70	173	2.5	36	69						7	16	2	0	2
	Exercise	75	283	3.9	52	75						9			0	2
	After medication															
	Rest	64	209	7.0	110	30							18	3		
	Exercise	70	316	8.7	124	36							19	5		
2	Before medication															
	Rest	47	169	2.7	57	60	84	42	62	27	10	16	28	2		
	Exercise	52	223	3.2	62	69	100	45	71	50	24	33	45	10		

The patient continued to take thyroid in doses of 0.065 and 0.09 Gm. daily and continued to feel well. She was observed again three years after her previous study, and the thyroid was omitted for one month. At the end of this time she had gained 8 pounds in weight, she was very much slowed up physically and mentally, and the skin had become much coarser and more dry. The radioactive iodine uptake was carried out using 100 microcuries of I^{131}, and twenty-four hours later the uptake by the thyroid gland was 1.2 per cent, which is an extremely low figure and indicative of myxedema. Thyroid was then resumed in previous doses, and she rapidly lost weight and regained her previous mental and physical improvement. Electrocardiograms and clinical examination during the time she was again myxedematous revealed no change from those done a few weeks before and were within the normal range. However, the heart size increased by 2.0 cm. in transverse diameter (orthodiagraphic measurement) when she was again in a hypothyroid state and rapidly became smaller under treatment.

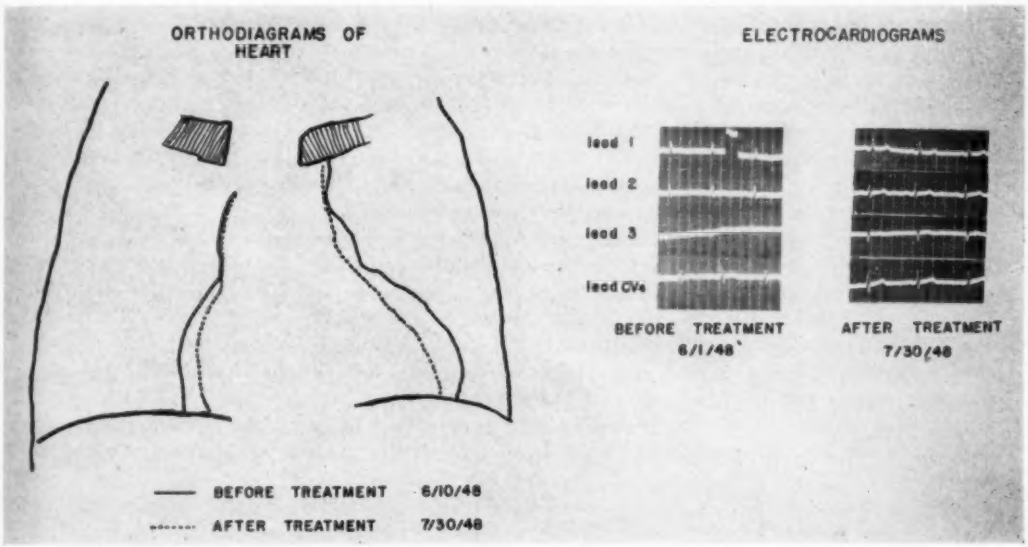

Fig. 1.—Orthodiagrams and electrocardiograms of Patient 1 before and after thyroid medication.

PATIENT 2.—A 63-year-old, white, greenhouse worker entered the hospital complaining of pain in the chest. He had had a thyroidectomy for hyperthyroidism in 1929 at another hospital. Following this, he took thyroid for three to four years because of symptoms of hypothyroidism, but at the end of this time he began to develop angina on exertion, so he discontinued the thyroid medication. Since the operation, he suffered from intolerance to cold, lack of perspiration, dry skin, and some mental and physical retardation. These symptoms were relieved while he was taking thyroid, but recurred when he ceased taking the drug. Recently there was some puffiness of the face and ankles, and the voice had become hoarse. For five years he had had increasing dyspnea on exertion, and over the same period the substernal distress on exertion, which disappeared when he stopped thyroid, recurred so that on entry it developed on very slight exercise. It was relieved by rest and by nitroglycerin. The remainder of the history was noncontributory.

On physical examination he was a well-developed man with a puffy face, dry skin which was diffusely pigmented, and sparse hair. There was no obvious venous distention, and the lungs were clear. The heart was somewhat enlarged to percussion; it was slow and regular; the sounds were

distant, and there were no murmurs. The arterial blood pressure was 95 mm. Hg systolic and 60 mm. Hg diastolic. There was slight thickening of the radial and brachial arteries to palpation. There was no demonstrable liver enlargement and no edema. The examination was otherwise negative.

Examination of the urine was negative on several occasions. The hemoglobin was 11.3 Gm. and the erythrocyte count 3.4 million. The blood Hinton was negative. An intravenous phenolsulfonphthalein test was normal with 30 per cent excretion of the dye in fifteen minutes. The blood nonprotein nitrogen was 35 mg. per cent and the fasting blood sugar 114 mg. per cent. The serum cholesterol was 465 mg. per cent on admission and 167 on discharge after seven weeks of thyroid medication. The circulation time from arm to tongue with magnesium sulfate was 40 seconds on admission and progressively dropped to 27, 23, and 16 seconds under treatment with thyroid.

Roentgenograms of the heart and lungs on admission showed congestive changes in the lung fields and a slightly enlarged heart shadow. A second teleroentgenogram taken ten days after treatment with thyroid extract revealed clear lung fields and a cardiac silhouette which was possibly a little smaller. An electrocardiogram on admission showed inverted T waves in all leads and a Q-S interval which was 0.11 second in duration.

Although the diagnosis of postoperative myxedema appeared to be established, certain special studies were performed to exclude adrenocortical insufficiency as well. The intramuscular injection of 2.5 mg. of adrenocorticotropic hormone resulted in a normal fall in the circulating eosinophils from 181 to 45 per cubic millimeter. An insulin tolerance test revealed a normal depression of the fasting blood sugar and a prompt rise afterwards (0.05 unit of insulin per kilogram of body weight given intravenously). The fasting blood sugar was 74 mg. per cent; at 15 minutes, 74 mg. per cent; at 30 minutes, 60 mg. per cent; at 60 minutes, 48 mg. per cent; at 120 minutes, 71 mg. per cent. These findings were considered sufficient evidence to allow the exclusion of Addison's disease in spite of the fact that the Wilder test was abnormal (371 mg. per cent of chloride). Less than 5 rat units of follicle-stimulating hormone were excreted in twenty-four hours.

In the hospital his condition remained virtually unchanged although he had no angina before the commencement of therapy. After three weeks of observation and five days after the cardiodynamic studies had been carried out, he was started on 0.015 Gm. of thyroid extract (U.S.P.) by mouth daily, and this was gradually increased until he was receiving 0.065 Gm. daily at the end of nineteen days. At this point he developed definite angina on slight effort and occasionally at rest, although in other ways he felt much better. The thyroid dosage was decreased to 0.05 Gm. daily for seven days, and then a dose of 0.065 Gm. was resumed. The angina gradually decreased although it was still present to some extent on discharge from the hospital after seven weeks of medication.

He was observed for three months after leaving the hospital and during this period was taking a daily dosage of 0.08 Gm. of thyroid. He was able to carry on as a helper in a parking lot. The angina had decreased very much in severity and frequency as compared to that from which he suffered prior to treatment. He still, however, developed mild, transient attacks on exertion equivalent to climbing one flight of stairs. The dyspnea had disappeared, and the symptoms of thyroid insufficiency were much diminished, although not entirely gone. He was sweating more than formerly.

Physical examination at the end of this period showed a man whose skin and hair were still somewhat dry, though less than formerly. Examination of the heart showed it to be unchanged. The blood pressure was 125 mm. Hg systolic and 60 mm. Hg diastolic. There was no pulmonary or peripheral congestion and no edema.

The electrocardiogram had not changed significantly. Circulation time by magnesium sulfate from arm to tongue had risen to 33 seconds. The basal metabolic rate was —33 per cent. The hemoglobin was 12.6 Gm. and the serum cholesterol 267 mg. per cent.

Studies made before the commencement of therapy revealed that the patient had a markedly diminished resting cardiac output with an increased peripheral utilization of oxygen, the arteriovenous oxygen difference being 60 c.c. per liter. The femoral arterial pressure was low, and the mean pulmonary arterial pressure and other intracardiac pressures were normal.

During exercise he was able to increase the cardiac output, but he showed a definite increase in the mean pulmonary arterial pressure, suggesting either a rigid pulmonary vascular bed or an increase in pressure transmitted back from the left auricle and pulmonary veins. There was also an increase in the right ventricular diastolic pressure, changes in which reflect alterations in right auricular and peripheral venous pressures. Such an increase suggests insufficiency of the right ventricle.[21]

These findings are similar to those encountered in patients with mild left- and right-sided heart failure. In such patients, however, the degree of lowering of the cardiac output is usually less and the increase in pulmonary artery and right ventricular systolic and diastolic pressures is usually greater than were those found in this patient.

PATIENT 3.—A 55-year-old, white, married housewife entered the hospital complaining of hemorrhoids. She had had known hypertension for four years, and at one time the systolic blood pressure was said to have been 240 mm. Hg. One year before entry, she developed headache, dizziness, and confusion, possibly due to a "shock." These symptoms cleared up promptly. There was some bleeding from the hemorrhoids for a year, and for about the same period of time she was hoarse and noticed intolerance to cold, lack of sweating, puffiness around the eyes, and a lump in the neck. There had been no chest pain or distress and no other cardiovascular symptoms. The menses were normal until she passed the menopause five years previously. Otherwise the history was noncontributory.

On physical examination she was an obese, middle-aged woman with a dry coarse skin. There was some peripheral edema. The tongue was enlarged and beefy. The thyroid was diffusely enlarged and nodular. No venous distention was noted. The heart was slightly enlarged, and there were Grade 2 apical and Grade 1 aortic systolic murmurs. The rate, rhythm, and sounds were normal except that the aortic second sound was accentuated. The blood pressure ranged between 150 and 170 mm. Hg systolic and 90 and 110 mm. Hg diastolic. The lungs were clear, and there was no edema. The rest of the examination was negative.

Repeated urinalyses were negative. The hemoglobin was 11.9 and 12.5 Gm. The serum cholesterol was 282 and 325 mg. per cent. The patient was started on 0.03 Gm. of thyroid extract (U.S.P.) daily three days before the hemodynamic studies were made, and after three weeks this was increased to 0.065 Gm. daily. The symptoms of hypothyroidism improved markedly, but after two months of this therapy she experienced for the first time substernal distress on exertion. There were no other symptoms, but the substernal pressure continued up to the time of the second study.

PATIENT 4.—A 69-year-old, deaf, white housewife had had symptoms for about nine years of gradual loss of weight (totaling 40 pounds), diffuse abdominal distress with belching and occasional vomiting, and severe headaches and constipation. These symptoms had gradually increased in severity. There were no cardiovascular symptoms.

On physical examination the patient was an elderly deaf woman with evidence of moderate arteriosclerosis and some kyphosis and emphysema. The heart was not enlarged to examination, the rate and rhythm were regular, and there were no murmurs. The blood pressure was 160 mm. Hg systolic and 70 mm. Hg diastolic. The lungs were clear; there was no venous congestion or edema, and the rest of the physical examination was negative.

On laboratory examination the urinalyses were negative, and the hemoglobin was 13 Gm. The serum cholesterol was 278 mg. per cent. There was no excretion of follicle-stimulating hormone in the urine. A tolerance test with 0.05 units per kilogram of body weight of insulin intravenously gave the following result: fasting blood sugar, 90 mg. per cent; 30 minutes, 40 mg. per cent; 60 minutes, 31 mg. per cent; 120 minutes, 49 mg. per cent.

The diagnosis was myxedema, probably of pituitary origin. The day following the hemodynamic studies, the patient was placed on therapy of 0.03 Gm. of thyroid extract (U.S.P.) daily, and the symptoms gradually improved. After ten days of treatment she was discharged and moved to another city so that follow-up studies could not be carried out.

PATIENT 5.—A 50-year-old, white, married housewife had had known myxedema since 1939 when she was first studied in this hospital. In 1931, after the birth of a child, she noticed dryness of the hair and skin, lack of sweating, easy fatigue, mental dullness, sleepiness, and severe constipation. She had another normal pregnancy in 1935 (? while on thyroid medication) and went through the menopause in 1942. She had been on thyroid treatment intermittently since 1931, and whenever she took the drug she experienced great relief of symptoms, but she would omit the treatment and the symptoms would recur. She had been in this hospital twice previously because of paralytic ileus. She had had no treatment for a year before the final admission. Two and one-half weeks before entry to the medical service, she was admitted to a surgical service with distention, vomiting, and increase in constipation. Intestinal obstruction was suspected, an exploratory laparotomy was performed, and only paralytic ileus was found. Following this operation the intestinal symptoms improved markedly, and she was transferred to the medical service for further study and treatment.

On physical examination at the time of transfer to the medical service, she was seen to be an obese woman with dry hair and skin, thick tongue, and pudgy fingers, deaf, hoarse, and mentally sluggish. The lungs were clear. The heart was questionably enlarged to percussion; the rate, rhythm, and sounds were normal, and there were no murmurs. There was no evidence of peripheral arteriosclerosis. The arterial blood pressure was 130 mm. Hg systolic and 70 mm. Hg diastolic. There was no edema, and the rest of the examination was noncontributory.

Several examinations of the urine were negative. The hemoglobin was 70 per cent (Sahli), and the erythrocyte count was 3.1 million. The serum cholesterol was 199 mg. per cent. The follicle-stimulating hormone excretion was 5 rat units in twenty-four hours. An insulin tolerance test with 0.05 unit per kilogram of body weight intravenously gave a normal result as follows: fasting blood sugar, 92 mg. per cent; 30 minutes, 55 mg. per cent; 60 minutes, 63 mg. per cent; 120 minutes, 80 mg. per cent; 180 minutes, 91 mg. per cent.

The patient continued to do well so far as the intestinal symptoms were concerned, but the other symptoms of myxedema were unchanged. The hemodynamic studies were carried out three days after transfer to the medical service, and two weeks later she was given 3.0 mg. of thyroxine intravenously. At about this time the vomiting recurred, she became increasingly distended, and in spite of vigorous medical therapy, she grew steadily worse and died after ten days of these aggravated symptoms.

Post-mortem examination revealed that there was intestinal obstruction of the terminal ileum due to adhesions from the former laparotomy wound, with generalized peritonitis.

The heart weighed 340 grams; the myocardium appeared normal in thickness. There were a few thin plaques in the mitral valves, and the aortic valves showed slight interadherence of the cusps. There were a number of large, soft atheromatous plaques in the coronary arteries, especially in the anterior descending branch, which produced a marked reduction of the lumina but no occlusion. There was no calcification. Microscopically, there was some fibrosis of the myocardium and one small focus suggesting an infarction. The adrenals were normal; the pituitary gland was normal grossly and also microscopically except for an increase in the chromophobe cells. No thyroid tissue could be identified grossly or histologically.

The results of the studies in these last three patients are considered together since they were similar, and clinically the patients resembled each other in many respects. They were all women past middle age. One (3) had definite arterial hypertension. Patient 4 suffered from what was believed to be pituitary myxedema; the other two had primary myxedema. None had symptoms or physical signs of heart failure. Six-foot teleroentgenograms showed the hearts to be slightly enlarged, and all had abnormal electrocardiograms. The electrocardiographic abnormalities were nonspecific, consisting of flattening or inversion of one or more of the T waves in the standard and precordial leads.

In all three patients the resting cardiac outputs were reduced, but this reduction was parallel to the lowering of the basal metabolic rates, since the oxygen

utilizations in the peripheral blood were within normal limits. The intracardiac pressures were normal. The plasma and blood volumes were reduced in the two patients in whom they were measured.

Studies were carried out in Patient 3 for a second time after she had been taking 0.065 Gm. of thyroid extract daily for eight weeks. At this time the symptoms of myxedema were improved, since she was mentally and physically less sluggish and the constipation had decreased. She had developed, however, a sensation of definite substernal pressure on exertion. At this time the heart size had decreased by 1.5 cm. according to teleroentgenographic measurement and was now within the normal limits. The electrocardiogram was unchanged. The oxygen consumption at this time was only slightly higher than at the first observation (218 versus 195 c.c. per minute), but the cardiac output had increased from 3.8 to 4.4 L. per minute. The increase in the stroke volume was even more evident (61 to 80 c.c.). The intracardiac pressures were still within the normal range, although the mean pulmonary arterial pressure was a little higher than at the first observation.

DISCUSSION

The findings in the five patients under study demonstrate that there is no uniformity in the response of the cardiovascular system to myxedema, although certain changes occurred in all cases.

The cardiac output was diminished in every instance. In three cases (3, 4, and 5) this reduction in output tended to parallel the reduction in oxygen consumption. Thus, the peripheral utilization of oxygen remained within normal limits, and, in this sense, the circulatory efficiency remained normal. Moreover, this was accomplished without increase in the intracardiac pressures—pulmonary artery, right ventricular, or right auricular—such as may occur in heart failure.[21] These three patients had no clinical evidence of heart failure while in the myxedematous stage. The entire circulatory response in these patients might be looked upon as a compensatory adjustment to the lowered oxygen consumption were it not for the enlargement of the heart shadow and electrocardiographic abnormalities present in all three. These are evidence of cardiac damage or of pericardial effusion. Since one (3) had definite arterial hypertension and all three may have had some degree of coronary atherosclerosis, it is impossible to ascribe these latter abnormalities with any certainty to the myxedema. However, the decrease in cardiac silhouette in Patient 3 following treatment suggests that myxedema was a factor in the cardiac enlargement. The electrocardiogram, however, showed no change after treatment.

In the other two patients the reduction of cardiac output was out of proportion to the decrease in oxygen consumption, and the absolute levels were of the order seen usually in severe heart failure or in shock. Patient 1 had symptoms suggesting cardiac insufficiency, i.e., dyspnea, orthopnea, and peripheral edema, and a suggestive elevation of the venous pressure on admission. Physiologic studies revealed findings which differed in many respects from those ordinarily occurring in heart failure. Patients suffering from left-sided heart failure usually show an elevation in the pulmonary artery pressure with a further increase during exercise and commonly are unable to increase their cardiac outputs during exer-

cise.[22] In patients with right-sided failure or with cardiac tamponade from pericardial effusion the right auricular and peripheral venous pressures are often elevated and increase further on exercise or on compression over the liver, and the circulating blood volumes are often high. None of these findings was present in this patient at the time the studies were made. And yet she was suffering from circulatory insufficiency. The clinical evidence of pulmonary congestion in this patient at a time when the pulmonary pressure relationships were normal suggests that congestion was on some other basis than an increase in hydrostatic pressure in the pulmonary circuit. It may have been due to the fact that the high protein edema characteristic of the myxedematous state also involved the lungs as well as the rest of the body. Under thyroid treatment the prompt return to normal of the heart size and the electrocardiogram and the re-establishment of the normal relationship between blood flow and oxygen consumption are evidences that the cardiovascular disturbance in this patient was due to myxedema, particularly in view of her age and the lack of evidence for any other etiological cause for heart disease. If anemia or thiamin deficiency had been factors in the production of the circulatory disturbance, one would expect an elevated and not a reduced cardiac output to be present. Moreover, the anemia had not changed at the time of improvement in the circulatory dynamics.

Patient 2, who also had a markedly reduced cardiac output, gave evidence clinically of coronary insufficiency by angina of effort. In his case the elevation of the mean pulmonary artery and ventricular diastolic pressures during exercise is a pattern to be found in left and right heart failure. Because of the patient's age, the indirect evidence for coronary atherosclerosis afforded by the angina, and the fact that it was not feasible to repeat in detail the studies after he was under treatment, it is impossible to evaluate the relative importance of coronary disease and of myxedema in producing these results. The course of the angina was unusual in this patient. It first occurred under thyroid medication and disappeared when this was stopped, to reappear at a later date while he was severely myxedematous. Recently it had diminished under thyroid medication. The latter development suggests that the improvement in cardiac efficiency and possibly in coronary blood flow resulting from this treatment more than overbalanced what increase there was in general, and probable cardiac, oxygen consumption. One factor in improved coronary blood flow may have been the increase in brachial blood pressure from an average of 85 mm. Hg systolic and 60 mm. Hg diastolic before treatment to 125 mm. Hg systolic and 60 mm. Hg diastolic after three months of therapy. It is of interest also that the symptoms of thyroid insufficiency as well as cardiac disability improved, although the basal metabolic rate remained low.

Three of the four patients in whom measurements of the circulating blood volumes were performed showed a reduction below the average normal figures. The anemia which all patients showed cannot be excluded as a factor in the diminished blood volumes. However, the reduction of blood volume which has been found in chronic anemia[21] has been due to a diminished red cell mass, the plasma volumes being normal or increased. In the three patients in this series with reduced total blood volumes the plasma volumes were also low. Also Patient 1,

who was restudied after treatment, then had an increase in blood volume, although the anemia remained unchanged. In Patient 2 the blood volume was not reduced, although it was not elevated above the normal for his size. Since it was not reduced, as is usual in myxedema, it may represent a relative increase in his case, and thus it may be comparable to the increases seen in heart failure. He had, in addition, other objective evidence of circulatory insufficiency.

The velocity of blood flow, as measured between two arbitrarily selected points in the vascular system, such as the antecubital vein and the small vessels of the tongue or face, was found to be retarded in one of the three patients (2) on whom such measurements were carried out, but in two (1 and 5) it was at the upper limit of normal and remained unchanged after treatment in one of these. This patient had the greatest reduction in cardiac output and showed a striking increase after thyroid medication. The explanation for this discrepancy is not certain, but it may possibly be found in a simultaneous alteration in two opposing factors influencing this circulation rate, the blood flow and the cross-sectional area of the pulmonary vascular bed. If the cross-sectional area of this vascular area, which is that which is chiefly involved in this circulation time, decreases or enlarges to a degree which parallels any change in blood flow, the velocity of blood flow through it will remain unaltered. In the patients with a normal circulatory rate the pulmonary vascular bed may have been reduced when their cardiac outputs were low and enlarged as they became normal. The comparative measurements of pulmonary vascular pressure are not inconsistent with such an explanation.

In every case the peripheral resistance in the systemic circulation was increased during the myxedematous stage as has been noted before.[5] In Patient 3 this increase could be due to vasospasm from the hypertension from which she was suffering, and it was not altered by therapy. In the other patients arterial hypertension was not present. Since these patients had reduced cardiac outputs and normal or reduced circulating blood volumes, the explanation must be in an absolute reduction in the cross-sectional area of the peripheral vascular bed, possibly compensatory to maintain an adequate pressure level in the face of the reduced blood volume and cardiac output. That this increased resistance is reversible is attested by its prompt reduction to normal after treatment in Patient 1. Elevation in the systemic blood pressure may occur in myxedema[24] and be relieved by treatment with thyroid. If the factors producing the increased peripheral resistance just described were excessively operative, then such an elevation in pressure might occur.

The calculated total pulmonary resistances were normal in three of the patients (1, 3, and 5). In one (2), who had other evidence of abnormal pulmonary hemodynamics, it was elevated, and it was elevated in Patient 4 who, in addition to myxedema, had clinical evidence of emphysema and moderate kyphosis, which it is known may be associated with pulmonary vascular disease. The total pulmonary resistance was calculated from the formula:

$$PR = \frac{\text{mean pulmonary artery pressure} \times 1332}{\text{cardiac output in c.c. per second}}$$

which disregards the pulmonary venous pressure. The lack of elevation in the pulmonary diastolic pressure in all cases (except Patient 2 during exercise) suggests that the pulmonary venous pressures were not elevated. Hence the increased resistance was on a precapillary basis suggesting that it was within the pulmonary circulation itself in all patients except 2 where the elevated pulmonary mean and diastolic pressures during exercise might have been caused either by an increase in precapillary resistance or by insufficiency of the left ventricle during strain or by a combination of these conditions.

This study confirms previous ones as to the alterations in cardiovascular dynamics which occur in myxedema. Because the myxedema itself may produce changes and because any degree of associated coronary atherosclerosis may also affect cardiac function, it is not surprising that such a variety of clinical patterns may occur in untreated myxedema and during therapy. Thus, cardiovascular insufficiency may be produced by myxedema itself, as in Patient 1, and be relieved by thyroid therapy. Coronary insufficiency may develop under treatment when the increased demand for oxygen cannot be met because of coronary narrowing due to arteriosclerosis. This was seen in Patient 3, who developed angina pectoris under therapy. If the beneficial effects of thyroid medication on the circulatory dynamics outweigh the coronary disease, then angina occurring during the myxedematous stage may be improved as in Patient 2.

The manifestations of cardiac insufficiency as seen in Patient 1 differ in many respects from those usually encountered in congestive failure. The clinical and physiologic manifestations of heart failure as commonly seen are dependent in a large part on the fact that there is a greater strain on one side of the heart as compared to the other, usually on the left ventricle. A balance between the two sides is maintained only by an alteration in pressure relationships and a tendency toward congestion in the vascular circuit behind the ventricle which is chiefly affected. In myxedema the entire myocardium is presumably affected, and both ventricles may dilate and fail in their function of maintaining an adequate cardiac output, without such congestive phenomena developing, at least as early manifestations. Although pericardial effusion may have been present in this patient, it is impossible to explain the abnormalities in circulatory physiology on this basis alone.

Artificially induced myxedema has been advocated as a form of therapy in cardiac patients with obstinate congestive failure or severe angina pectoris on the theoretical grounds that the work of the heart will be lessened because of the reduced metabolic rate of the body. The fact that in myxedema the cardiac output may be reduced out of proportion to the reduction in oxygen consumption, together with the marked enlargement of the cardiac silhouette (whether due to dilatation or to pericardial effusion) which may occur, as well as the electrocardiographic abnormalities, raises the question whether therapeutic hypothyroidism may not at times have deleterious effects on the heart which outweigh the benefit of a reduced metabolism. An additional problem in this connection, on which this investigation sheds no light, is the effect such a procedure may have in aggravating coronary atherosclerosis.

SUMMARY

Hemodynamic studies of the circulation are reported in five patients with myxedema and in two of these after treatment with thyroid. The varying circulatory responses to the myxedematous state are pointed out, and the complicating factors of associated arteriosclerosis are emphasized. The studies indicate that, although frequently changes in the circulation are parallel to reduction of oxygen consumption, the blood flow may be depressed out of proportion to the oxygen needs of the body. This finding, judged in conjunction with the development of cardiac enlargement and electrocardiographic abnormalities, is evidence of damage to the heart and of circulatory insufficiency.

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STUDIES OF THE CIRCULATORY DYNAMICS AT REST IN MITRAL VALVULAR REGURGITATION WITH AND WITHOUT STENOSIS

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ALTHOUGH stenosis of the mitral valve frequently exists without associated regurgitation,[1] regurgitation rarely occurs without stenosis. For this reason, little is known of the effects of mitral regurgitation itself (1) on the right and left sides of the heart and on the pulmonary circulation and (2) in the production of symptoms or on the clinical course of these patients. Similarly, the effects on the circulation of combined regurgitation and stenosis are ill defined. With the advent of intracardiac valvular surgery,[2,3] the circulatory implications, diagnosis, quantitation, surgical relief, and effects of surgical production of regurgitation have become problems of pressing concern. It is the purpose of this report to present, through the use of hydraulic principles[4] and the technique of cardiac catheterization, an analytical study of the circulatory dynamics of mitral regurgitation with and without stenosis.

Wiggers and Feil[5] showed in experimental animals how total left ventricular discharge rapidly increased within a few beats so as to maintain aortic pressure and blood flow as well as regurgitant flow when an acute mitral insufficiency is produced. In these experiments, the pressures in the pulmonary vascular circuit were relatively unaffected. These findings were confirmed by Lanari and Molins,[6] who, in addition, found that if the regurgitation were severe enough, left atrial pressures rose to such high levels that gross pulmonary edema developed with eventual death of the animal. Both groups of workers described high spiking pressures in the left atrium coincident with ventricular systole.

Keys and Friedell[7] first demonstrated the magnitude of regurgitation by determining both roentgenkymographic (total) and Fick (aortic) stroke outputs. They found that regurgitation varied from 25 to 100 per cent of the aortic stroke output but seldom exceeded that figure. Stewart and associates[8] observed only slightly decreased cardiac outputs in mitral insufficiency and stenosis and normal venous pressures in the absence of congestive failure. Draper and co-

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workers[9] reported very low peripheral blood flows in mitral insufficiency and stenosis. This latter group found pulmonary artery and "capillary" pressures to be elevated and right ventricular failure a not uncommon finding.

These studies have shed light on some important aspects of valvular regurgitation, but the major values concerning which little still is known are the size of the regurgitant valve defect, the amount of regurgitant blood flow, and the magnitude of the load on the left ventricle. Given these values, one can make both a practical and a theoretical analysis, not only of the effects of regurgitation on the circulation, but also of the factors governing the magnitude of regurgitation and the maintenance of aortic blood flow.

Among the important questions to be answered are: What are the effects of regurgitation on the two circulations? How do the dynamics of regurgitation alone and regurgitation with stenosis differ from the dynamics of pure stenosis? How much regurgitation can be consistent with life? Is the left ventricle overtaxed in this disease? Are the effects of regurgitation of an order indicating the need for specific surgery as is the case with stenosis? What compensations does the body make to this disease, and how may therapy be adjuvant to these compensations? To answer some of these questions, a complete picture of the overall physiology of regurgitation must be reconstructed. To do this, we have employed hydraulic principles. The various assumptions and indirect measurements introduced a certain degree of error, as discussed elsewhere.[4] The immediate need for a better understanding of mitral regurgitation was so great, however, as to encourage this presentation of our results because, despite these errors, the findings have indicated the pattern of the disease. The values derived from the hydraulic formulas are meant to serve as estimates, not as precise calculations of the true values.

CLINICAL MATERIAL AND METHODS

Twelve patients with mitral valvular regurgitation were studied a total of fifteen times. One of the patients, M. S., was believed to have pure congenital mitral insufficiency; the other eleven had both regurgitation and stenosis. One of these, patient E. D., had pure tight mitral stenosis prior to mitral valvuloplasty and has been reported elsewhere.[10] Following operation, the mitral valve was widened, but regurgitation was produced. This afforded an opportunity to study the dynamics of newly acquired mitral insufficiency. None of these patients had demonstrable aortic disease; four (E. L., E. D., M. D. [second study], and J. S.) had physiologic but not clinical evidence for tricuspid regurgitation, and one, A. D., had tricuspid stenosis. None was believed to have active rheumatic fever at the time of study.

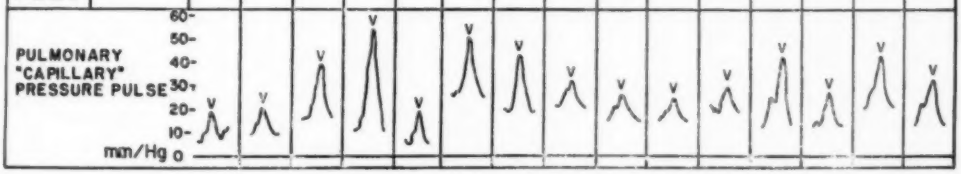
Mitral regurgitation was suspected clinically (Table I) from the nature of the apical systolic murmur, the presence of combined or left ventricular hypertrophy by electrocardiogram, and paradoxical left atrial pulsations by fluoroscopy. The presence of a systolic regurgitant jet was noted in each of the patients subjected to mitral valvuloplasty.* Finally, regurgitation was denoted physiologi-

*By Dr. D. E. Harken.

cally by the disappearance of the "descent of the base" and increased magnitude of the V wave in the pulmonary "capillary" pressure tracing (Table I). All patients included in this series had at least one and usually two other signs of regurgitation in addition to a systolic murmur.

TABLE I. CLINICAL AND PHYSIOLOGIC EVIDENCE OF MITRAL REGURGITATION IN PATIENTS STUDIED

PATIENTS		M.S.	L.L.	E.D.	E.L.	E.L.*	A.D.	A.D.*	M.D.	M.D.*	D.N.	F.K.	E.S.	L.C.	J.S.	C.J.
GRADE OF APICAL SYSTOLIC MURMUR		III	IV	III	V	III	III	III	II	II	III	III	V	III	II	III
LEFT ATRIUM BY FLUOROSCOPY	ENLARGED	++	+++	+++	+++	+++	+++	+++	++	++	+++	+++	+++	+++	+++	+++
	PARADOXICAL PULSATION	yes	yes	yes	yes	yes	no	no	yes	yes	yes	yes	no	no	yes	no
VENTRICULAR HYPERTROPHY BY ELECTROCARDIOGRAM	RIGHT	no	yes	yes	yes	yes	no	no	yes	yes	no	no	yes	no	no	no
	LEFT	yes	yes	no	yes	yes	no	yes	no	no	no	no	no	no	no	no
PULMONARY "CAPILLARY" PRESSURE PULSE																



Enlargement of the left atrium was scaled as follows: + = slight; ++ = moderate; +++ = marked.

In the pulmonary "capillary" pressure pulses, which were traced to scale from the original pressure curves, V equals the wave of ventricular systole. The small crest on the ascending limb is the c wave of mitral valve closure. A waves of auricular systole were noted only in patients M. S. and F. K. because the other patients were fibrillating.

*Observations were made on patients E. L., A. D., and M. D. three weeks after mitral valvuloplasty, except that in A. D. the electrocardiographic observations were made eight months after operation.

In Table II, the patients are arranged according to the size of the forward mitral valve area and classified as proposed by the New York Heart Association.[11] The mitral valve orifice areas were measured at autopsy or digitally at operation in six patients for a total of nine studies. Estimation of the size of the orifice of the mitral valve by digital palpation at the time of operation has been found to agree within 0.1 or 0.2 cm.^{2} with the area measured at autopsy in seven cases. The mitral valve area for body size and age was assumed in patient M. S., who had pure mitral regurgitation on a congenital basis.

Patients were studied in a fasting state or an hour or more following a light breakfast of black coffee, toast, and jam. Cardiac catheterization was carried out in the usual fashion. Pulmonary "capillary" pressure was measured as described elsewhere[12]; both phasic and mean pressures were recorded. This pressure was used as an index of left atrial pressure[13] and was believed to be slightly

TABLE II. PHYSIOLOGIC DATA ON PATIENTS

PATIENT	A-P DIAMETER OF CHEST (CM.)	BODY SURFACE AREA (SQ. M.)	CLINICAL CLASSIFICATION	RHYTHM	FORWARD MITRAL VALVE AREA ($CM.^2$)	REGURGITANT MITRAL VALVE AREA ($CM.^2$)	ARTERIAL OXYGEN SATURATION (PER CENT)	OXYGEN CONSUMPTION (C.C. PER MINUTE PER SQ. M.)	A-V OXYGEN DIFFERENCE (C.C. PER LITER)	LEFT VENTRICULAR OUTPUT (L. PER MINUTE PER SQ. M.)			PULSE RATE (PER MINUTE)	LEFT VENTRICULAR STROKE OUTPUT (C.C. PER BEAT PER SQ. M.)		
										AORTIC	TOTAL	REGURGITANT		AORTIC	TOTAL	REGURGITANT
Pure Mitral																
M.S.	17	1.47	II	SR	4.0	0.4	98	187	47	4.0	6.6	2.6	109	37	61	24
Mitral Regurgitation																
L.L.	18	1.49	III	AF	3.0‡	0.9	100	190	63	3.0	6.8	3.8	69	43	99	56
E.D.	20	1.44	III	AF	1.5	0.4	97	130	68	1.9	4.4	2.5	98	19	45	26
E.L.*	20	1.40	IV	AF	1.1	0.7	97	161	114	1.4	4.5	3.1	91	15	49	34
E.L.†		1.36			2.3	0.6	98	121	63	1.9	4.7	2.8	86	22	55	33
A.D.*	18.5	1.55	IV	AF	1.3	0.5	88	158	78	2.0	4.8	2.8	130	15	37	22
A.D.†					1.9	0.7		151	64	2.3	5.8	3.5	92	25	63	38
M.D.*	20	1.90	III	AF	1.6	0.3	99	144	48	3.0	4.5	1.5	96	31	47	16
M.D.†					1.7	0.4	95	159	64	2.5	4.1	1.6	120	21	34	13
D.N.	21	1.61	III	AF	1.6	0.6	97	139	59	2.4	4.7	2.3	55	44	86	42
Subaverage										2.3	4.9	2.7	93	26	57	31
F.K.		1.44	III	SR			99	175	49	3.5			120	29		
E.S.	22	1.45	IV	AF			95	159	53	3.0			82	37		
L.C.	16	1.43	IV	AF			98	147	60	2.4			72	33		
J.S.	20	1.55	IV	AF			98	165	51	3.2			94	34		
C.J.	16	1.52	III	AF				127	58	2.2			65	34		
Average							97	154	64	2.5			91	29		

SR = sinus rhythm.
AF = auricular fibrillation.
*Study performed before mitral valvuloplasty.
†Study performed two to four weeks after mitral valvuloplasty.
‡Measured at autopsy; all others measured by digital palpation during mitral valvuloplasty.
§Right ventricular diastolic pressure.

WITH MITRAL REGURGITATION

FORWARD MITRAL VALVE FLOW (C.C. PER DIASTOLIC SECOND)	DIASTOLIC FILLING PERIOD (SECONDS PER BEAT)	SYSTOLIC EJECTION PERIOD (SECONDS PER BEAT)	PRESSURES (MM. HG)						RESISTANCES (DYNES SECOND CM.$^{-5}$)			VENTRICULAR PRESSURE WORK (KG. M. PER MINUTE PER SQ. M.)	
			PULMONARY ARTERY MEAN	PULMONARY "CAPILLARY" MEAN	PULMONARY "CAPILLARY" PHASIC	BRACHIAL ARTERIAL MEAN	BRACHIAL ARTERIAL SYSTOLIC MEAN	RIGHT ATRIAL MEAN	PULMONARY ARTERIOLAR	TOTAL PULMONARY	TOTAL PERIPHERAL	RIGHT	LEFT
Regurgitation													
329	0.27	0.28	15	12	18/6	77	83	2	41	203	1043	0.75	7.4
and Stenosis													
247	0.60	0.27	19	12	21/9	93	110	3	125	338	1652	0.69	10.2
185	0.35	0.26	42	21	36/13	102	117	4	600	1200	2915	1.0	7.1
150	0.46	0.20	61	24	55/11	97	108	5	1480	2440	3875	1.1	6.7
156	0.48	0.22	27	10	19/5	68	90	4	523	830	2090	0.63	5.8
228	0.25	0.21	41	37	52/26	103	118	8§	103	1056	2660	0.95	7.8
270	0.36	0.29	34	26	43/17	83	94	4§	178	756	1844	0.99	7.4
233	0.38	0.25	37	27	33/20	107	135	4	140	519	1500	1.4	8.4
223	0.29	0.21	30	23	26/15	108	120	5	119	510	1840	0.90	6.8
206	0.76	0.34	24	18	25/15	87	110	8	126	505	1830	0.55	7.1
211	0.42	0.25	35	22			111					0.91	7.5
			39	22	35/18	77		3	267	612	1208	1.8	
			57	24	47/11	92		9	600	1037	1671	2.1	
			26	21	32/18	82		6	114	594	1875	0.69	
			35	32	43/21	89		4	48	560	1423	1.4	
			27	23	37/13			6	97	654		0.66	
			36	23	36/15	92		5	304	829	2045	1.1	

less than true pulmonary capillary pressure.[12] The catheter was then withdrawn to the pulmonary artery in the region of the bifurcation. A No. 21 needle connected with a saline drip was introduced into the brachial artery. When pulse and respiratory rates were stable, the effective or aortic cardiac output was determined by the direct Fick principle. Expired air was collected for three minutes in a Douglas bag. The volume was measured in a Tissot spirometer. Oxygen and carbon-dioxide concentrations were measured by the Haldane-Henderson method. In most experiments, oxygen alone was measured by the Pauling oxygen analyzer. From previous studies of Haldane analysis of expired air, a mean correction factor of 1.007 was derived for converting expired volume to inspired volume under resting conditions.[14] The volume of oxygen inspired was calculated as per cent inspired oxygen times volume of expired air times 1.007. Midway during the collection of the expired air, blood samples were withdrawn from the pulmonary and from the systemic arteries simultaneously and analyzed for oxygen content, capacity, and saturation by the method of Van Slyke and Neill,[15] and arteriovenous oxygen differences were calculated. Pressures were recorded in the pulmonary artery and systemic artery simultaneously immediately after the withdrawal of blood samples. Phasic and mean pressures were recorded with electromanometers*[16] which recorded on a multi-channel, direct-writing oscillograph. A saline manometer was used for checking mean pressures but not for analytical purposes. Mean pressures were obtained by electrical integration at the time of recording. Brachial artery systolic mean pressures were obtained by planimetric integration of the pressure tracings. The zero point for all pressures was 10 cm. anterior to the back with the patient in the recumbent or semireclining position.

The mitral valve regurgitant orifice area (MRA) was calculated as described elsewhere[4] by the following formula:

$$MRA = \frac{(MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5}) - CO}{SEP \times 36 \sqrt{BA_{sm} - \text{"PC"}}}$$

where MVA = forward mitral valve area in cm.^{2}
DFP = diastolic filling period in diastolic seconds per minute
31 = empirical constant
"PC" = pulmonary "capillary" mean pressure as an index of left atrial mean pressure in mm. Hg
5 = assumed left ventricular diastolic pressure in mm. Hg
CO = aortic cardiac output in c.c. per minute
SEP = systolic ejection period in systolic seconds per minute
36 = empirical constant
BA_{sm} = brachial arterial systolic mean pressure in mm. Hg.

The total left ventricular output (Fm) was calculated as follows[4]:

$$Fm = MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5}$$

and the regurgitant output (Fr) was calculated as follows[4]:

*Sanborn Company, Cambridge, Mass.

$$Fr = Fm - CO$$

where Fm = total left ventricular output
CO = aortic output.

The rate of forward mitral valve flow (MVF) was calculated as follows[17]:

$$MVF = \frac{Fm}{DFP}$$

Resistances were calculated according to the Poiseuille equation, where resistance equals $\frac{\text{pressure gradient}}{\text{rate of blood flow}}$. Pulmonary arteriolar resistance was calculated as follows:

$$R = \frac{PA_m - \text{“}PC_m\text{”}}{CO} \times 1332 \text{ dynes seconds cm.}^{-5}$$

The total pulmonary resistance was calculated as follows:

$$R' = \frac{PA_m - 0}{CO} \times 1332 \text{ dynes seconds cm.}^{-5}$$

The total peripheral resistance was calculated as follows:

$$R'' = \frac{BA_m - 0}{CO} \times 1332 \text{ dynes seconds cm.}^{-5}$$

where PA_m = pulmonary arterial mean pressure in mm. Hg
$\text{“}PC_m\text{”}$ = pulmonary “capillary” mean pressure in mm. Hg
BA_m = brachial arterial mean pressure in mm. Hg
CO = cardiac output in c.c. per second
1332 = factor for converting mm. Hg to dynes per cm.^{2}

The work of the right and left ventricles was estimated by calculating pulmonary and systemic work against pressure as follows[13]:

$$W_R = \frac{(CI_R \times 1.055)\ [(PA_m - RA_m) \times 13.6]}{1000} \text{ Kg. M. per minute per sq. m.}$$

$$W_L = \frac{(CI_L \times 1.055)\ [(BA_m - 5) \times 13.6]}{1000} \text{ Kg. M. per minute per sq. m.}$$

where W_R = right ventricular pressure work in Kg. M. per minute per sq. m.
W_L = left ventricular pressure work in Kg. M. per minute per sq. m.
CI_R = right ventricular output = Fick cardiac output in liters per minute per sq. m.
CI_L = left ventricular output = regurgitant + Fick cardiac output in liters per minute per sq. m.
1.055 = specific gravity of blood

PA_m = pulmonary arterial mean pressure in mm. Hg
RA_m = right auricular mean pressure in mm. Hg
BA_{sm} = brachial arterial systolic mean pressure in mm. Hg
5 = assumed left ventricular mean diastolic pressure in mm. Hg
13.6 = factor to convert millimeters of mercury to millimeters of water.

Observations of the pulmonary circulation were made in all twelve patients. In only seven of this number was it possible to study the dynamics of the left ventricle and the systemic circulation, because only in these seven was the forward mitral valve area known, which was necessary for making the various computations. Because we were mainly concerned with over-all circulatory function rather than specific cardiac function, the cardiac minute volume rather than volume delivery per stroke was used in describing the various interrelationships in mitral valvular disease. As will be seen, many of the factors limiting blood flow in mitral disease are extracardiac in origin.

RESULTS

1. Pure Mitral Regurgitation.—Patient M. S. was considered to have mitral regurgitation on a congenital basis. Pertinent data are seen in Tables I and II and Figs. 1 and 2. A forward mitral valve area of 4.0 cm.^{2} was assumed in this patient on the basis of age and body size. The calculated mitral regurgitant area was 0.4 cm.^{2}

Oxygen consumption per square meter of body surface area was within normal limits (Fig. 1). The effective cardiac output or aortic blood flow and tissue oxygen extraction per cubic centimeter of blood likewise were normal (Fig. 1).

Dynamics of the left side of the heart: To maintain the normal blood flow, the total output of the left ventricle, which includes the amount of blood regurgitated into the left atrium, was greatly increased over the normal. The left ventricular cardiac index was 6.6 L. per minute per square meter, of which 4 L. were discharged forward and 2.6 L. were discharged backward every minute (Fig. 1). This unusually large blood flow was handled by an increase in the ventricular stroke volume to a value exceeding that seen in normal patients at rest.[18] The rate of flow of blood through the mitral valve during diastole was increased from the normal resting average of 150 to 200[19] to 325 c.c. per diastolic second.

Brachial arterial mean and systolic mean pressures were somewhat lower than normal, and the total peripheral resistance was normal. Left ventricular pressure work was definitely but not markedly increased (7.4 kg.M. per minute per square meter) from the normal average of 5.0 (Fig. 2). This patient had left ventricular hypertrophy by electrocardiogram.

Dynamics of the right side of the heart: Right ventricular output was normal. Mean pulmonary "capillary" pressure was at the upper limit of normal (Fig. 1). The V wave in the pulmonary "capillary" tracing, from crest to trough, was 12 mm. Hg in height (Table I). Most of the pressure elevation was due to the area under the large V wave. The trough or end diastolic pressure in the pulmonary "capillary" tracing was 6 mm. Hg. Since there was no stenosis of the mitral

valve, it seems probable that the pressure at this point was in equilibrium with the left ventricular end diastolic pressure. Being normal, it indicated normal left ventricular function, despite a large stroke volume. Mean pulmonary arterial pressure was within normal limits, as were both the pulmonary artery-pulmonary "capillary" pressure gradient and the pulmonary arteriolar resistance (Fig. 2). The right ventricular filling pressure and work were also observed to be normal (Fig. 2).

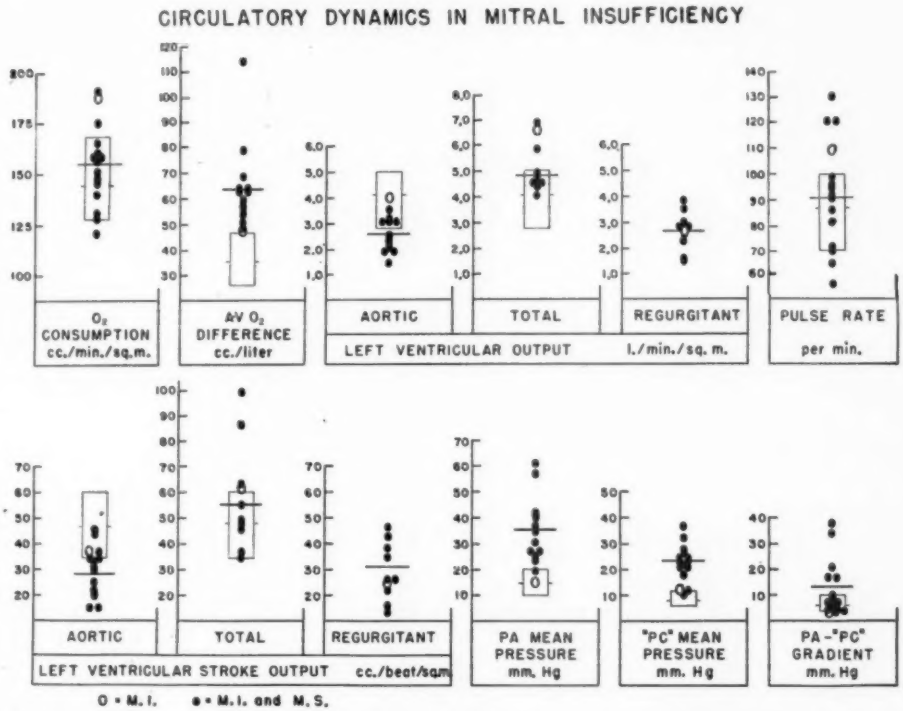


Fig. 1.—The solid dots represent mitral insufficiency and stenosis. The single open circle represents pure mitral regurgitation. In columns 4, 5, 8, and 9, only ten observations were available for plotting because only in these patients was the forward mitral valve area known.

Summary: The over-all circulatory compensation in this patient with apparently pure mitral regurgitation was as follows: A normal bodily blood flow was maintained at the expense of a large increase in left ventricular stroke output which was delivered at a normal filling pressure. The remainder of the stroke output regurgitated into the left auricle. The pulmonary circuit was essentially unaffected by the large flow load of the left side of the heart because little atrial pressure elevation was necessary to increase flow through the large mitral orifice.

Clinical findings: Patient M. S. complained of only one symptom and that was excessive fatigue and weakness on exertion. She had no dyspnea or evidence for right ventricular failure. The left atrium was enlarged and exhibited paradoxical systolic pulsations by fluoroscopy. She had left ventricular hypertrophy by electrocardiogram.

2. Mitral Regurgitation and Stenosis.—Data on eleven patients with mitral insufficiency and stenosis are presented in Tables I and II and Figs. 1 and 2. Three of these patients (E. L., A. D., and M.D.) were studied twice, once before and again about three weeks after mitral valvuloplasty. Forward mitral valve areas ranged from 1.1 to 3.0 cm.^{2} in six patients in whom this area was measured. The calculated regurgitant areas in these individuals ranged from 0.3 to 0.9 cm.^{2}

Oxygen consumption per square meter was maintained within normal limits in all these patients (Fig. 1). This was accomplished by reciprocal adjustments between the existing level of aortic cardiac output, which was reduced, and tissue oxygen extraction per cubic centimeter of blood (arteriovenous oxygen difference), which was increased (Fig. 1).

The reduction of the effective (aortic) cardiac output in this group of patients appeared to be related in inverse fashion to the mitral valve stenotic area (Fig. 3).

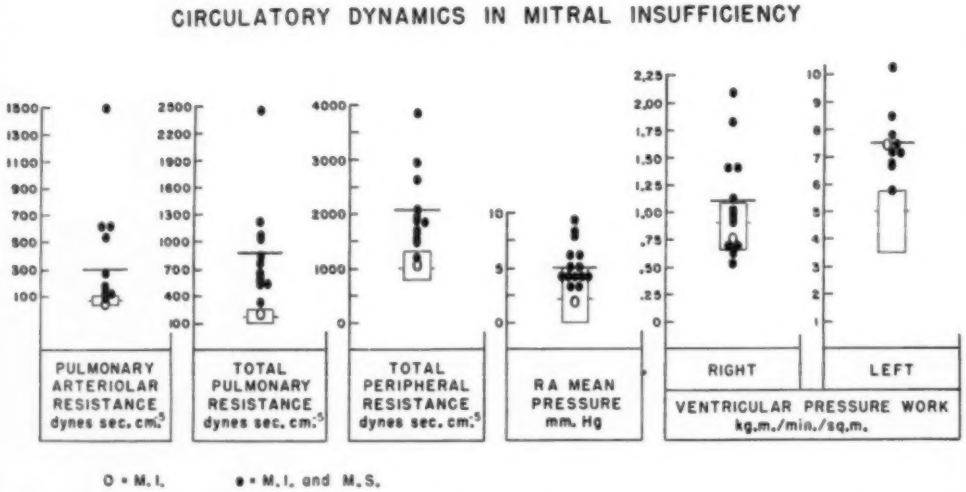

CIRCULATORY DYNAMICS IN MITRAL INSUFFICIENCY
PULMONARY ARTERIOLAR RESISTANCE dynes sec. cm.$^{-5}$
TOTAL PULMONARY RESISTANCE dynes sec. cm.$^{-5}$
TOTAL PERIPHERAL RESISTANCE dynes sec. cm.$^{-5}$
RA MEAN PRESSURE mm. Hg
RIGHT
LEFT
VENTRICULAR PRESSURE WORK kg.m./min./sq.m.
O = M.I.
● = M.I. and M.S.

Fig. 2.—The solid dots represent mitral insufficiency and stenosis. The single open circle represents pure mitral regurgitation. In column 6, only ten observations were available for plotting because only in these patients was the forward mitral valve area known.

Dynamics of the left side of the heart: The dynamics of the left side of the heart were studied in the first six patients with mitral regurgitation and stenosis in whom complete calculations of total, regurgitant, and aortic blood flows could be made (Table II). The subaverages in Table II were derived solely from the data on these six patients as were the appropriate plots in Figs. 1, 2, 3, and 4.

The total left ventricular output per square meter of body surface area was somewhat but not markedly elevated (Fig. 1). In no patient was the total left ventricular blood flow below the normal average of 4.2 L. per minute per square meter found in this laboratory under similar conditions of study.[18] The total left ventricular cardiac output bore (1) a rough inverse relationship to the degree of mitral stenosis (Fig. 3), that is, the more severe the stenosis, the less the total ventricular inflow and output, and (2) a direct relationship to the size of the regurgitant defect and degree of regurgitation (Fig. 3). There was no apparent re-

lationship between aortic output and the degree of regurgitation. Although there was some variation, average regurgitant flow (Table II) equalled about 50 per cent of the total left ventricular output and therefore was about the same, on the average, as aortic flow in all but patient M. D., giving the left ventricle an average "forward flow efficiency" of about 50 per cent. Regurgitant blood flow varied directly as the area of the regurgitant defect (Fig. 3).

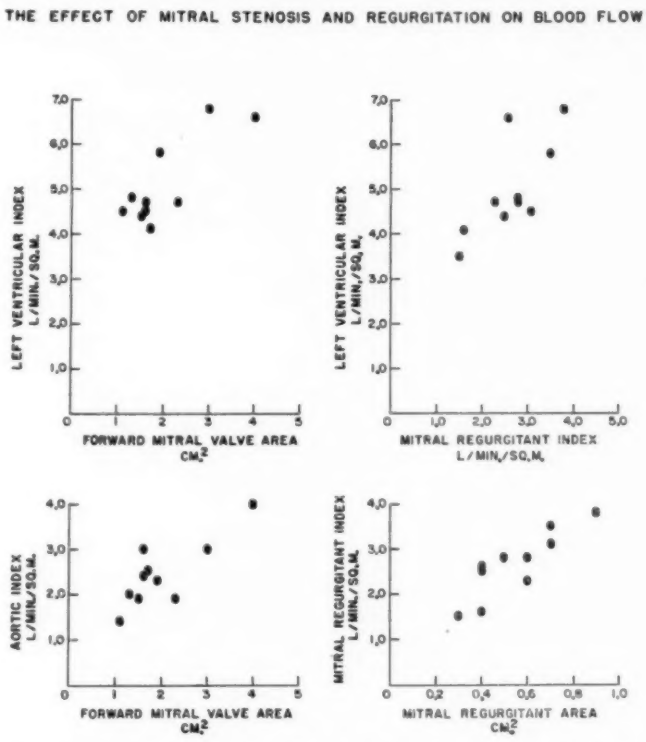

THE EFFECT OF MITRAL STENOSIS AND REGURGITATION ON BLOOD FLOW
LEFT VENTRICULAR INDEX L/MIN./SQ.M.
FORWARD MITRAL VALVE AREA CM.²
MITRAL REGURGITANT INDEX L/MIN./SQ.M.
AORTIC INDEX L/MIN./SQ.M.
MITRAL REGURGITANT AREA CM.²

Fig. 3.—The relation of total, aortic, and regurgitant outputs to one another and to their respective orifice areas.

The average rate of forward flow through the mitral valve in diastole was 211 c.c. per diastolic second (Table II) which was almost the same (201 c.c. per second) as the flow rates seen in patients with similar degrees of pure mitral stenosis (Table III). The patients with mitral insufficiency, however, tended to have a greater minute volume of inflow (total left ventricular output in Tables II and III) than similar patients with pure mitral stenosis. This resulted because in seven of the nine studies where complete data were available the duration of ventricular diastole for a given pulse rate was longer than normal because systolic ejection was shorter than normal (Fig. 4). Auricular fibrillation was present in all nine studies.

Brachial arterial pressures varied somewhat but were within the normal range in all, with the possible exception of patient M. D. The calculated total peripheral resistance was increased on the average and bore an inverse logarithmic relationship to the aortic output (Fig. 5). Left ventricular work against pressure

TABLE III. PHYSIOLOGIC DATA ON PATIENTS WITH PURE MILD MITRAL STENOSIS

PATIENT	CLINICAL CLASSIFICATION	MITRAL VALVE AREA (CM.²)	RHYTHM	OXYGEN CONSUMPTION (C.C. PER MINUTE PER SQ. M.)	A-V OXYGEN DIFFERENCE (C.C. PER LITER)	CARDIAC INDEX (L. PER MINUTE PER SQ. M.)	PULSE RATE (PER MINUTE)	STROKE INDEX (C.C. PER BEAT PER SQ. M.)	MITRAL VALVE FLOW (C.C. PER DIASTOLIC SECOND)	DIASTOLIC FILLING PERIOD (SECONDS PER BEAT)	SYSTOLIC EJECTION PERIOD (SECONDS PER BEAT)	MEAN PRESSURES (MM. Hg)					RESISTANCES (DYNES SECOND CM. $^{-5}$)			WORK OF VENTRICLES AGAINST PRESSURE (KG. M. PER MIN. PER SQ. M.)	
												PULMONARY ARTERY	PULMONARY "CAPILLARY"	BRACHIAL ARTERY	BRACHIAL ARTERY SYSTOLIC	RIGHT AURICLE	PULMONARY ARTERIOLAR	TOTAL PULMONARY	TOTAL PERIPHERAL	RIGHT VENTRICLE	LEFT VENTRICLE*
J. D.	I	2.5	SR	153	30	5.2	100	52	303	0.31	0.29	25	19	91	109	9	51	212	775	1.2	7.8
J. F.	II	1.6	SR	149	39	3.8	72	54	192	0.47	0.36	32	21	92	110	9	135	394	1130	1.3	5.7
L. B.	II	1.4	SR	138	42	3.3	90	37	172	0.31	0.36	24	20	65	77	4	67	400	1082	0.95	3.4
L. C.	IV	1.4	SR	160	48	3.3	104	34	200	0.25	0.33	75	27			9	711	1110		3.1	
J. M.	II	1.3	SR	139	53	2.7	108	25	176	0.23	0.33	33	25			0	145	600		1.3	
Gr.	III	1.1	SR	207	45	4.6	100	46	175	0.40	0.20	42	32	82	110	8	114	480	936	2.3	6.9
				157	51	3.0	120	25	175	0.23	0.27	51	38			3	221	866		2.1	
F. C.†	II	2.3	SR	149	35	4.3	94	51	217	0.40	0.24	20	13	90	107	3	68	195	828	1.95	6.3
Averages				157	43	3.8	100	41	201	0.33	0.30	38	22	84	103	6	189	532	950	1.7	6.0

SR = sinus rhythm.

*Calculated using brachial arterial systolic mean pressure.

†This case, not reported previously,[10] had a body surface area of 1.92 sq. m.; anteroposterior diameter of the chest 19 cm.; arterial oxygen saturation 98 per cent.

was increased (Fig. 2) due to the large blood flows, although only about 50 per cent of the work performed was effective in propelling blood forward.

Three patients (L. L., E. L., and A. $D._2$) had left ventricular hypertrophy by electrocardiogram (Table I). Two of these three had the highest total left ventricular blood flows seen in the group.

Dynamics of the right side of the heart: Studies of the dynamics of the right side of the heart were made in the total group of eleven patients for a total of fourteen observations. Right ventricular output, identical with aortic output, was reduced (Fig. 1), although there were a few cases (patients L. L., M. D., F. K., and E. S.) in which the output was within normal limits.

COMPARISON OF THE DURATION OF DIASTOLE IN PATIENTS WITH MITRAL REGURGITATION AND STENOSIS TO THE NORMAL CURVE OF DIASTOLE

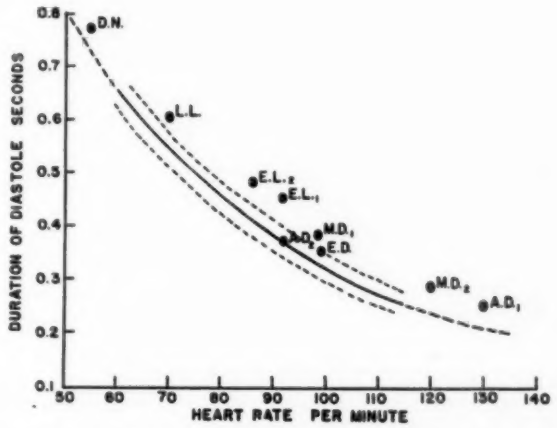


Fig. 4.—Above are plotted the values for the duration of left ventricular diastole in the nine patients with mitral insufficiency, mitral stenosis, and auricular fibrillation in whom the forward mitral valve area was known. They are compared to the curve of the duration of left ventricular diastole derived by the same indirect method of measurement on a brachial arterial tracing in normal individuals with sinus rhythm. Note that diastole was prolonged in the majority of the fibrillating patients.

Mean pulmonary "capillary" pressure ranged from nearly normal to considerably elevated levels with an average of 23 mm. Hg (Fig. 1). This pressure tended to be in the same range as in patients with similar degrees of pure mild mitral stenosis,[10] and the relationship of pressure and flow across the mitral valve tended to be similar (Tables II and III). In patients L. L. and E. $L._2$, this pressure was within the upper limits of normal; each had a moderately large forward mitral valve. Pulmonary "capillary" pressure was 18 mm. Hg in patient D. N., who had a stenotic area of 1.6 $cm.^2$ but a very slow pulse rate and a long period for diastolic filling. Pulmonary "capillary" pressure was within a narrow range between 21 and 27 mm. Hg in nine of these thirteen studies, and the forward valve areas which were known in six of these cases varied from 1.1 to 1.9 $cm.^2$ In patient A. D., this pressure was 37 mm. Hg. This patient had moderately severe mitral stenosis and a tachycardia of 130, which accounted for this extreme elevation of pulmonary "capillary" pressure.[19]

The pulmonary "capillary" pressure pulse in each case showed a V wave of increased amplitude (Table I). This V wave is mainly a reflection of regurgitated blood during ventricular systole and its decline the result of the large diastolic run-off into the left ventricle as the mitral valve opens. The height of the V wave is determined, however, not only by the degree of regurgitation, but also by the volume-elasticity properties of the left atrium, the degree of atriovenous congestion as measured by the height of the pulmonary "capillary" mean pressure, and the rate of pulmonary venous inflow. For example, patient L. L. had

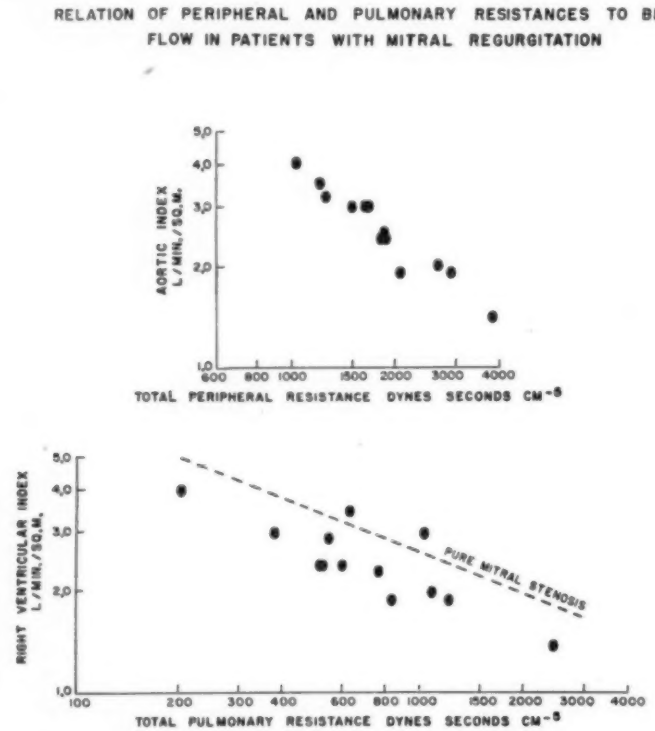

RELATION OF PERIPHERAL AND PULMONARY RESISTANCES TO BLOOD FLOW IN PATIENTS WITH MITRAL REGURGITATION
AORTIC INDEX L/MIN./SQ.M.
5.0
4.0
3.0
2.0
1.0
600 800 1000 1500 2000 3000 4000
TOTAL PERIPHERAL RESISTANCE DYNES SECONDS CM⁻⁵
RIGHT VENTRICULAR INDEX L/MIN./SQ.M.
PURE MITRAL STENOSIS
100 200 300 400 600 800 1000 1500 2000 3000 4000
TOTAL PULMONARY RESISTANCE DYNES SECONDS CM⁻⁵

Fig. 5.—In the uppermost figure, aortic cardiac output is plotted against the systemic circuit resistance. An inverse straight-line logarithmic relationship is observed.

In the lower figure, right ventricular output is plotted against total pulmonary resistance. An inverse straight-line logarithmic relationship is observed which apparently is parallel to but lower than that seen in pure mitral stenosis.

a pulmonary "capillary" pressure pulse of only 12 mm. Hg at a low mean pressure, although regurgitation was considerable, 3.8 L. per minute per square meter. On the other hand, patient A. D. had considerably more atriovenous congestion as evidenced by a mean pressure of 37 mm. Hg. Here the pulse pressure was 26 mm. Hg with regurgitation of 2.8 L. per minute per square meter. Thus, while the large V wave is often indicative of the *presence* of regurgitation, it is by no means a good measure of the *degree* of regurgitation.

Pulmonary arterial pressure and the pulmonary arterial-pulmonary "capillary" pressure gradient were not markedly different on the average from values seen in patients with similar degrees of pure mitral stenosis (Tables II and III).

The pulmonary arteriolar resistance was normal or only slightly increased in eleven observations, moderately increased in three, and markedly increased in one observation (Fig. 2). The average arteriolar resistance in general was not significantly different from that seen in patients with a similar degree of pure stenosis. Patient E. D. should be excluded from this consideration here because the mitral insufficiency was of only two weeks' duration, and the increased vascular resistance was probably related to the mitral stenosis present before surgery.

Total pulmonary resistance varied from as low as 338 to as high as 2,440 dynes seconds cm.$^{-5}$ (Fig. 2). When this resistance was plotted against right ventricular cardiac index, an inverse relationship was obtained similar to but lower than that seen in pure mitral stenosis (Fig. 5).[10] The total pulmonary resistances were higher than those seen in patients with similar degrees of mitral stenosis because most of the pulmonary pressure was expended in maintaining pressure on the mitral valve rather than in propelling blood through the lungs. When this resistance was greater than 600 dynes seconds cm.$^{-5}$, the cardiac index was observed to be less than 2.5 L. per minute per square meter in six out of eight observations.

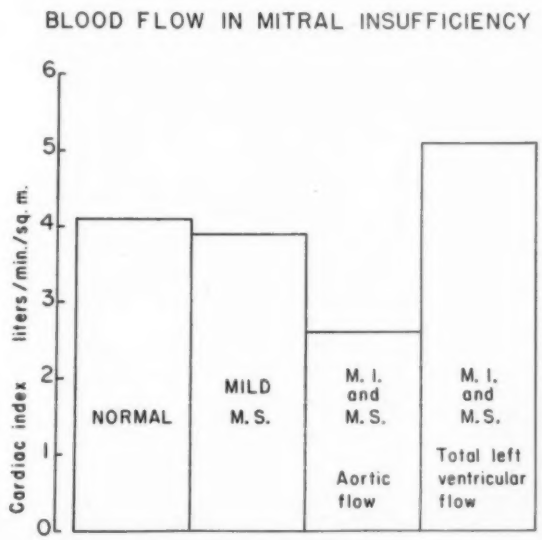


Fig. 6.—In this diagram are drawn values for blood flow in normal individuals and in patients with pure mitral stenosis of similar degree to those in columns 3 and 4 with combined regurgitation and stenosis. While total left ventricular blood flow actually exceeded the normal value, the amount escaping to the body, the aortic output, was lower than could be accounted for by the mitral stenosis alone.

Right ventricular diastolic filling pressure averaged 5 mm. Hg, which was at the upper limit of normal (Fig. 2). Right ventricular work on the average was at the upper limit of normal and thus was much less than the degree of work performed by patients with a similar degree of pure mitral stenosis (Tables II and III, Fig. 2). This resulted because, although the pulmonary pressures were equal in the two groups, the amount of blood ejected per minute by the right ventricle was decreased in those with both regurgitation and stenosis. The work load tended to be increased when right ventricular output approached normal levels.

Five patients had right ventricular hypertrophy by electrocardiogram. E. D. should be excluded from this consideration because right ventricular hypertrophy was more properly related to the preoperative mitral stenosis.[10] Of the four patients with total pulmonary resistances over 1,000 dynes seconds cm.$^{-5}$, three had right ventricular hypertrophy.

Summary: When mitral regurgitation was associated with stenosis, certain circulatory patterns developed. The total left ventricular output was somewhat increased (Fig. 6), depending inversely on the degree of mitral stenosis and directly on the degree of mitral regurgitation. Aortic blood flow was usually decreased (Fig. 6), depending on the available total left ventricular output and the degree of regurgitation. Oxygen consumption was maintained at normal levels in the face of a decreased aortic output by an increase in tissue oxygen extraction from the blood. The elevated pressures in the pulmonary circuit were almost entirely dependent on the degree of mitral stenosis unless there was an elevation of left ventricular diastolic pressure for any cause, as with severe regurgitation. The degree of pressure elevation was identical to that seen in patients with similar degrees of pure stenosis. Evidence was presented to show that a normal left ventricle could tolerate a considerable degree of regurgitation without failure.

Clinical findings: None of these patients had disabling dyspnea (Table IV). Paroxysmal nocturnal dyspnea and hemoptysis were likewise uncommon. All the patients, however, had weakness and easy fatigability of moderate to marked degree. Except for patient A. D., who had tricuspid stenosis, hepatomegaly of significant degree was present in only two patients, one of whom had a total pulmonary resistance of 2,440 dynes seconds cm.$^{-5}$ Peripheral edema was similarly infrequently found to any extent.

TABLE IV. CLINICAL FINDINGS IN PATIENTS WITH MITRAL REGURGITATION

	M. S.	L. L.	E. D.	E. L.	A. D.	M. D.	D. N.	F. K.	E. S.	L. C.	J. S.	C. J.
Severity of dyspnea	0	++	++	++	++	++	++	++	++	++	+	+
Paroxysmal nocturnal dyspnea	0	0	0	+	0	0	+	0	+	0	0	+
Hemoptysis	0	0	0	0	0	++	0	0	0	0	0	0
Fatigue	++	++	++	++	++	+	++		+	+++	+++	+++
Hepatomegaly	0	0	++*	++	+++†	0	±	±	±	0	0	±
Edema	0	±	0	0	+++†	0	0	0	++	±	±	0

+ = slight
++ = moderate
+++ = marked
*This patient had had hepatomegaly prior to mitral valvuloplasty.
†This patient had associated tricuspid stenosis, which probably explained the marked hepatomegaly and edema.

An apical systolic murmur was present in each patient and varied in intensity from Grades 2 to 5. All the patients had markedly enlarged left atria, and in

seven of eleven there was paradoxical pulsation fluoroscopically. The relative infrequency of univentricular hypertrophy can be seen in Table I.

DISCUSSION

The circulatory abnormalities of mitral regurgitation are consequent upon the fact that during systole the left ventricle is confronted by two competing orifices through which it may discharge, the aortic and mitral valves. In order to maintain life, an adequate supply of blood at normal perfusion pressures must be delivered to the systemic circuit. With every systole, however, a certain volume of blood regurgitates into the left atrium. Thus, either total left ventricular stroke volume must increase or aortic output must decrease. In either case, the pumping pressure of the ventricle cannot fall far below normal if tissue perfusion is to be maintained. An equilibrium develops between total, regurgitant, and peripheral blood flow.

When mitral stenosis is associated with regurgitation, to this equilibrium between blood flows is added the equilibrium between pulmonary "capillary" pressure and total left ventricular flow.[10] Thus the pressure and flow balance in mitral regurgitation and stenosis is more complicated than that seen in pure mitral stenosis. If this balance is upset, however, the end results are the same as in mitral stenosis, namely pulmonary edema on the one hand and peripheral circulatory collapse on the other. The role of the various factors influencing pressure and flow in this disease will be analyzed in the following discussion.

In the patients with mitral regurgitation and stenosis, oxygen consumption is maintained at normal levels by reciprocal adjustment of aortic blood flow and tissue oxygen extraction from the blood. In our patient with pure regurgitation, aortic flow and tissue oxygen extraction were normal. As observed by Draper and associates,[9] effective aortic blood flow was in general decreased but to varying degrees below the normal level, depending on a series of complicated interrelated circulatory adjustments.

Effect of Regurgitation on the Left Ventricle and Systemic Circuit

1. Total Left Ventricular Output.—In the patient with pure mitral regurgitation, a normal aortic blood flow was maintained but only at the expense of a large increase in total left ventricular output. If there was an associated stenosis, as in our other patients, the total left ventricular output was found to be only somewhat greater than the normal with a consequent reduction in aortic output.

2. Left Ventricular Work Against Pressure.—As a result of the somewhat increased total left ventricular output, the left ventricle had to perform an increased amount of pressure work. The greatest amount of work was performed when the forward mitral valve area was greatest and therefore blood flow through the valve greatest. In the absence of mitral stenosis (patient M. S.) ventricular inflow was not limited by a narrowed mitral valve, and flow was increased to the level necessary to maintain normal aortic blood flow. Conversely, the presence of mitral stenosis of any degree imposed a limit on diastolic inflow into the ventricle, and, as a result, the total left ventricular blood flow and

pressure work were not so markedly elevated as might ordinarily be expected. Stenosis tended to spare the left ventricle, while adding to the burden of the right ventricle.[10]

How much of the left ventricular work was effective in terms of aortic delivery depended on the factors governing the regurgitant and aortic outflows. For example, in patient M. D., who had a small regurgitant orifice, 67 per cent of the pressure work was effective as contrasted with patient E. L., in whom only 31 per cent of the work was effective because the regurgitant leak was much larger.

3. Left Ventricular Failure.—There is some evidence that ventricular function may be relatively unaffected by considerable increases in flow load, as indicated by normal diastolic filling pressure. This has been seen frequently in patent ductus arteriosus, with left ventricular blood flows as high as 18.3 L. per minute, yet pulmonary "capillary" pressures were within normal limits[20] in aortic insufficiency[21] and in atrial septal defect where right ventricular filling pressures were normal in the absence of mitral stenosis or an atrophic left ventricle despite flows as high as 20 L. per minute.[20] Because the ventricular ejection pressures are normal, the load in mitral insufficiency is entirely that of an increased left ventricular stroke volume, the magnitude of which, if anything, has been overestimated by our techniques.[4] The results of the study, however, indicate only moderately increased blood flows. Whether this increase can be accomplished at normal diastolic filling pressure in the absence of myocarditis is at present unsettled, no direct observations of left ventricular diastolic pressures having been made in this laboratory. Some information may be obtained from observations of the pulmonary "capillary" diastolic pressure. This is the pressure just prior to the "c" wave. It is the lowest point during diastole and most closely approaches left ventricular diastolic pressure.[20] Because most of ventricular filling normally occurs early in diastole, by the end of diastole this pressure has reached a virtual equilibrium with left ventricular diastolic pressure. When mitral stenosis is present or when the rate of diastolic inflow is increased as with tachycardia, the pulmonary "capillary" diastolic pressure may not necessarily come into equilibrium with the ventricular diastolic pressure and therefore may be higher.

Table II contains values of the pulmonary "capillary" diastolic pressure for each patient. In patients M. S., L. L., and E. L., the values were 6, 9, and 5 mm. Hg, respectively, with total left ventricular outputs of 6.6, 6.8, and 4.7 L. per minute per square meter. These findings indicate (1) that the left ventricular diastolic pressure remained normal with increased flows in these individuals, as is seen in other diseases,[20,21] and (2) that this degree of regurgitation was handled normally by the left ventricle. In the other patients who had severe mitral stenosis or tachycardia, no conclusions could be drawn because the pulmonary "capillary" diastolic pressure had presumably not entered into equilibrium and was higher than the left ventricular diastolic pressure. When failure is present, it is probably related more to active myocardial disease than to the moderately elevated work load, which was readily tolerated by a number of the patients in this group.

It has been demonstrated both experimentally[6] and clinically following mitral valvular surgery[22] that when severe valvular regurgitation is produced, gross pulmonary edema results. In animals, it could be shown that this was usually associated with an elevated left atrial and left ventricular diastolic pressure. By analogy, severe regurgitation applied suddenly in man probably results in acute left ventricular failure from the large flow load. Whether true ventricular failure results from gradually applied regurgitation is not known, but it probably does occur when the regurgitant load is excessively large.[20]

Summary: The presence of mitral stenosis restricts the volume of left ventricular inflow and therefore output. The small increases in total output seen with mild to moderate regurgitation are usually well tolerated by the left ventricle in the absence of acute rheumatic carditis or other complicating disease. When there is severe regurgitation as can occur only when the stenosis is mild, the left ventricle may fail, and the patient may have severe pulmonary symptoms as a result.

4. Left Ventricular Hypertrophy.—Left ventricular hypertrophy may occur electrocardiographically in patients with mitral regurgitation. Four of the twelve patients here reported had left ventricular hypertrophy. None had other apparent cause for this finding. There was no correlation between the degree of left ventricular work performed at rest and electrical evidence of left ventricular hypertrophy. Those (M. S., L. L., A. $D._2$) with the largest total left ventricular outputs, however, did have left ventricular hypertrophy. Patient A. D. actually developed left ventricular hypertrophy during the year following mitral valvuloplasty, when the valve was widened and total blood flow increased. Patient E. L. had combined ventricular hypertrophy with a total left ventricular output of 4.5 L. per minute per square meter which was about the average total output of the three patients with calculated left ventricular outputs who did not have left ventricular hypertrophy. In summary, then, left ventricular hypertrophy by electrocardiogram was not a constant finding in patients with mitral regurgitation. When present, it could be inferred that total left ventricular output was usually considerably increased.

5. The Relation of Total Peripheral Resistance to Aortic Output.—Total peripheral resistance was increased in several of our patients with mitral insufficiency and stenosis and bore an inverse logarithmic relationship to the aortic output (Fig. 5). An increased peripheral resistance has been observed in congestive failure,[23,24] in mitral stenosis,[10] and in cor pulmonale.[20] In these diseases, there is a primary reduction in cardiac output due either to poor cardiac function or to obstruction to blood flow through the pulmonary circuit. Similarly in mitral insufficiency and stenosis the decreased aortic cardiac output is related to the mitral valvular lesion itself, the level of pulmonary arteriolar resistance, and myocardial failure. It is assumed here as in the previously mentioned diseases that the increased peripheral resistance is secondary to the reduction in aortic output and is designed primarily to maintain perfusion pressure to vital organs.

Effect of Mitral Regurgitation on the Pulmonary Circuit and Right Ventricle

1. Pulmonary "Capillary" Pressure.—In pure mitral regurgitation, the mitral valve orifice is so large that only slight increases in atrial pressure head are needed to maintain the high normal to increased flow through the mitral valve. This may be demonstrated if the mitral valve area equation is solved for "PC" as an index of left atrial pressure[19]:

$$\text{"PC"} = \frac{\text{MVF}^2}{31^2 \times \text{MVA}^2} + 5$$

where "PC" = pulmonary "capillary" pressure in mm. Hg
MVF = forward mitral valve flow in c.c. per second
31 = empirical constant
MVA = stenotic mitral valve area in cm.^{2}
5 = assumed left ventricular diastolic pressure in mm. Hg.

In patient M. S., in whom the mitral valve area was considered to be 4 cm.^{2}, pulmonary "capillary" pressure, as an index of left atrial pressure, was increased only 4 mm. Hg over the level required to maintain a normal cardiac output in the absence of regurgitation, although the valvular flow rate was increased one and one-half over the normal rate. It is unlikely, therefore, that pure regurgitation places a major load on the pulmonary circulation unless left ventricular failure develops because, in the absence of a congested atriovenous circuit, the regurgitation wave by itself is too small and of too short duration to elevate the mean pressure in the pulmonary circuit by more than 5 or 6 mm. Hg.

When stenosis and regurgitation are associated, pulmonary "capillary" pressures rise to varying degrees. From the formula just mentioned it may be seen that the level of pulmonary "capillary" pressure depends on (1) the degree of mitral stenosis (MVA) and (2) the valvular flow rate, which controls in part the total left ventricular output. This in turn is affected by (a) the degree of regurgitation (Fig. 3) and (b) the functional state of the left ventricle.

The level of pulmonary "capillary" pressure was almost the same as that seen in patients with similar degrees of mitral stenosis (Tables II and III). As shown by the formula above, the level of pulmonary "capillary" pressure was related directly to the total left ventricular output at any given degree of stenosis. In pure mitral stenosis, aortic output is equal to total left ventricular output, while in mitral regurgitation it is only a fraction thereof. The aortic flow must be maintained at a level compatible with tissue demands, and only in this respect is aortic flow in equilibrium with pulmonary "capillary" pressure.

A close correlation between rises in pulmonary "capillary" pressure to 35 mm. Hg or more and the occurrence of clinical pulmonary edema has been demonstrated in this laboratory.[10,19] In contrast to the group of patients with pure mitral stenosis, six of whom were in pulmonary edema with elevated pulmonary "capillary" pressures at the time of cardiac catheterization, only one of the patients (A. D.) with associated mitral insufficiency had a pulmonary "capillary" pressure in excess of 35 mm. Hg, and none developed clinical pulmonary edema.

None of the patients gave a history of paroxysmal pulmonary edema. These clinical findings were probably due to the fact that pulmonary "capillary" pressure seldom reached transudation levels. This was so because (1) none of the patients had tight mitral stenosis and the level of pressure behind the mitral valve was directly dependent on the degree of anatomic stenosis and (2) mitral insufficiency per se did not lead to markedly elevated pulmonary "capillary" pressure unless left ventricular failure developed.

2. Pulmonary Arteriolar Resistance.—It has been shown by Dexter and associates[18] that as pulmonary "capillary" pressure approaches and exceeds 25 mm. Hg, the pulmonary artery-pulmonary "capillary" pressure gradient and pulmonary arteriolar resistance tend to rise. The average level of pulmonary "capillary" pressure in these patients was 23 mm. Hg. In this group, only two patients (E. L.$_{1,2}$ and E. S.) had a markedly elevated pulmonary arteriolar resistance. In all the others, the resistance was no higher than 267 dynes seconds cm.$^{-5}$ Patient E. D. is excluded from this consideration because in her case the elevation of resistance was probably related to the severe mitral stenosis present preoperatively. The level of arteriolar resistance was in general similar to that seen in patients with similar degrees of pure stenosis. The lack of elevation of this resistance in these two groups of patients was related to the fact that there was only a moderate elevation of pulmonary "capillary" pressure which, as discussed, is dependent for its level mainly on the severity of the mitral stenosis and the presence or absence of left ventricular failure.

3. Right Ventricular Ejection Pressure.—As described elsewhere,[14] pulmonary arterial mean pressure was used as an index of right ventricular mean systolic ejection pressure in the absence of pulmonic stenosis. The effect of mitral insufficiency and stenosis on this ejection pressure was variable. In patient L. L. there was mild mitral stenosis, a normal pulmonary arteriolar resistance, no left ventricular failure, and a marked degree of mitral regurgitation. As a result, the right ventricular ejection pressure was normal. Patient E. L. had a moderate degree of mitral stenosis, moderate regurgitation, no evidence of left ventricular failure, and marked pulmonary arteriolar narrowing. The right ventricular ejection pressure was markedly increased.

Summary: As in pure mitral stenosis, right ventricular ejection pressures depended on the degree of obstruction present in the lesser circuit resulting from the mitral stenosis, pulmonary arteriolar resistance, left ventricular failure, and to only a slight extent from the mitral insufficiency itself.

4. Right Ventricular Work Against Pressure.—In contrast to patients with similar degrees of pure mitral stenosis[10] (Table III), right ventricular pressure work was not greatly increased over the normal. Pressure work depends both on the pressure head to be created and on the amount of blood to be moved. The increased left atrial pressure of mitral valvular disease means that there must be a further elevation of right ventricular pressure not only to exert pressure on the mitral valve, but also to maintain blood flow to that point. Pressure losses between right ventricle and left atrium were not observed to be greatly increased, however, for two reasons: (1) Pulmonary arteriolar resistance was not often

greatly increased in these particular patients, and (2) pulmonary blood flow was often markedly decreased. As a result, frictional flow losses through the pulmonary circuit were not large. Most of the right ventricular work was done in maintaining an increased pressure head on the mitral valve orifice to fill the left ventricle with blood. Increases in work, however, did occur when the pulmonary blood flow approached normal levels, as in patients M. D., F. K., E. S., and J. S. None of the other patients showed an increase in work of any magnitude.

Thus, by leading to a reduced aortic blood flow at an elevated left atrial pressure head, regurgitation tended to decrease the flow load placed on the right ventricle and hence to decrease its work output. In a sense regurgitation tends to spare the right ventricle.

5. Right Ventricular Failure.—Right ventricular failure, as denoted by an increased right atrial mean pressure,[14] was not a common finding in our patients. Only three had a marked elevation of filling pressure at the time of study. As in the case of mitral stenosis,[10] there was no strict correlation between either the amount of pressure work performed or the total pulmonary resistance and the level of right atrial pressure.

In the presence of severe myocardial damage, even a normal work load or total pulmonary resistance may precipitate failure, and conversely a normal myocardium may fail if the work load or total resistance is greatly increased.[25] When the load is only moderately increased over a long period of time, hypertrophy may keep pace with the increase and the load handled without necessarily producing a rise in diastolic filling pressure. Such was seen in patients with mitral regurgitation and stenosis, where the load was sometimes increased yet filling pressure was frequently within the limits of normal.

An elevated diastolic filling pressure can be attributed to (1) an acutely increased work load, as with tachycardia or exercise, (2) myocardial damage, as with acute rheumatic carditis, or (3) failure of hypertrophy to keep up with the load. Given any of these three conditions, a ventricle already partially compromised by a chronically elevated pressure or flow load may well go into failure. The exact causes for the elevated filling pressures seen in patients A. D., D. N., and E. S. cannot be stated with certainty. In patient A. D., however, who also had tricuspid disease, the tachycardia of 130 was probably sufficient to cause mild right ventricular failure. In the others, the reasons were not immediately apparent.

Summary: Right ventricular failure was not a common finding in our patients. The presence or absence of ventricular failure apparently depended not only upon the load placed on the heart, which was not excessive in those patients, but also on the state of the myocardium and whether or not ventricular hypertrophy could keep up with the load.

6. Right Ventricular Hypertrophy.—Only five of the patients (L. L., E. D., E. L., M. D., and E. S.) had electrocardiographic evidence of right ventricular hypertrophy, and E. D. had hypertrophy prior to operation due to mitral stenosis. It has been demonstrated in mitral stenosis that right ventricular hypertrophy

is frequently seen when the resting total pulmonary resistance exceeds 1,000 dynes seconds cm.$^{-5}$; [26] the total resistance serves as an index of the chronic pressure load against which the right ventricle pumps. Three of the five patients (E. D., E. L., and E. S.) had a total pulmonary resistance over 1,000 dynes seconds cm.$^{-5}$ Conversely, of the four patients in the series who had an elevated total pulmonary resistance (E. D., E. L., A. D., and E. S.) three had right ventricular hypertrophy. The fourth patient, A. D., had a tachycardia during the study. As a result, the calculated total pulmonary resistance of 1,056 dynes seconds cm.$^{-5}$ could not be considered as the average resting pulmonary load, which probably was much lower at a normal heart rate.

While an increased pressure load usually led to right ventricular hypertrophy, the fact that two patients did not have greatly increased loads indicated that hypertrophy could develop for other causes, at present unknown. However, the relative infrequency of right ventricular hypertrophy in mitral insufficiency and stenosis was probably related to the fact that the daily work load and stimulus for hypertrophy were not markedly increased over the normal in many of these patients.

Regulation of Blood Flow

The initial "set" of cardiac output originates probably from peripheral mechanisms. The exact nature by which cardiac output is regulated is unknown, but it does seem certain that some system peripheral to the heart chambers, possibly the brain or the coronary artery system, is responsible for controlling cardiac action and the rate of the venous return. The initial "set" of peripheral blood flow may be altered, however, by numerous factors which tend to limit cardiac function in the presence of mitral regurgitation. These are (1) the left ventricular volume and pumping capacity, (2) the effect of mitral disease, (3) the total pulmonary resistance, (4) factors regulating aortic output peripheral to the left ventricle, and (5) myocardial function.

If the initial setting for aortic blood flow were greater than normal in a patient with mitral regurgitation, as with pregnancy,[27,28] thyrotoxicosis,[29,30] anemia,[31,32,33] fever,[34] emotion,[35,36,37] and exercise,[14,38,39] then the deleterious effect of each of these factors on the circulation would be augmented, and the circulation would be that much more compromised. In the following discussion, the peripheral "set" for blood flow will be assumed normal to start with.

1. The Left Ventricular Volume and Pumping Capacity.—Despite the presence of regurgitation, no patient in this series had a total stroke volume larger than 99 c.c. per beat per square meter. This was in part due to the effect of mitral stenosis on total stroke output (see following).

Up to a point, the left ventricle can maintain a normal aortic output in addition to severe regurgitation, as was seen in patient L. L. If the regurgitant volume were overwhelmingly large, however, the ventricle might not be able to receive and discharge the total volume of blood necessary to keep up a normal aortic stroke index of about 45 c.c. per beat per square meter. Either left ventricular dilatation and death in pulmonary edema would result or aortic output

would decrease to shock levels. Usually, an equilibrium develops whereby total stroke volume is increased but within physiologic limits and aortic output is decreased but tissue supply is maintained. The degree of decrease in aortic output would depend on many factors, among them the required total left ventricular stroke volume, the suddenness with which the increased left ventricular flow load is applied, and peripheral circulatory demands, i.e., the "set."

Just what is the maximum resting stroke volume which may be delivered by the ventricle is variable and not at all predictable. Stroke volumes of 90 to 130 c.c. per beat per square meter have been seen in patients with patent ductus arteriosus[20] and complete heart block[40,41] without apparent ventricular failure.

The left ventricular volume capacity in mitral insufficiency may well be much larger than the normal because the load is applied gradually over the course of years, and the ventricle may accommodate more blood with gradual dilatation and hypertrophy. In patient M. S., for example, the left ventricle pumped 6.6 L. per minute per square meter, yet, as judged from the pulmonary "capillary" diastolic pressure, the left ventricular diastolic filling pressure was only 6 mm. Hg. The time factor with development of compensatory hypertrophy is important in the circulatory adaptation to regurgitation.[42] This, however, does not necessarily hold true for acute mitral regurgitation. The reason patients frequently die when significant mitral regurgitation is produced at the time of mitral surgery[22] or by rupture of a papillary muscle is that the left ventricle is unable to handle the sudden demand for the large volumes of blood necessary to maintain both peripheral and regurgitant outputs. Left ventricular failure may supervene with elevation of pressure in the lungs and pulmonary edema. With or without actual ventricular failure, aortic output may fall to extremely low levels with peripheral circulatory collapse and the clinical picture of shock, all as a result of a sudden increase in load on the left ventricle due to regurgitation. Thus, the degree of regurgitation, the suddenness of its appearance, and the capacity of the left ventricle to handle the increased volume influence the level of aortic output. The difference between acute and chronic regurgitation lies in the fact that in the former the load is handled by an increased diastolic filling pressure and dilatation, while the latter is handled usually by muscular hypertrophy.[42]

Summary: The ability of the left ventricle to dilate, receive, and discharge without failure the increased volume of blood needed when there is regurgitation is an important factor regulating aortic output.

2. The Effect of Mitral Valvular Disease.—

A. Mitral regurgitation: The factors affecting the volume of regurgitation are best illustrated by solving the regurgitant orifice formula for Fr:[4]

$$MRA = \frac{Fr}{SEP \times 36 \sqrt{BA_{sm} - \text{“}PC_m\text{”}}}$$

$$Fr = MRA \times SEP \times 36\sqrt{BA_{sm} - \text{“}PC_m\text{”}}$$

where Fr = regurgitant output in liters per minute
MRA = mitral valve regurgitant orifice area in cm.^{2}
SEP = systolic ejection period in systolic seconds per minute
36 = empirical constant
BA_{sm} = brachial arterial mean systolic pressure in mm. Hg
"PC_m" = pulmonary "capillary" mean pressure in mm. Hg

Regurgitant volume varies directly as regurgitant area and duration of flow (systolic ejection) and directly as the square root of the systolic pressure head. The effect of regurgitant valve area on the degree of regurgitation is demonstrated in Fig. 3. As in any hydraulic system, the flow increases in direct proportion to an increase in orifice size. Hence, the degree of regurgitation and secondarily the left ventricular output (Fig. 3) are partly dependent on the size of the regurgitant area. Note, for example, the large volume seen in patient L. L. as compared to patient M. D., explained mainly by the difference in regurgitant area.

The reason the comparatively small regurgitant areas seen in all of our cases are of such significance is because of the extremely high pressures applied to them during ventricular systole. These pressures are so high that life cannot exist if the regurgitant defect is very large. The transvalvular pressure gradient is altered by changes in either intraventricular or intra-atrial pressure. Patient M. D., who had mild systemic hypertension, had a pressure gradient of 108 mm. Hg, while in patient A. D. with a similar intra-atrial pressure, the gradient was only 68 mm. Hg. The effects of such differences of pressure on flow are not so striking as they would at first glance appear, however, because flow varies as the square root of the pressure head. Nevertheless, regurgitation will be increased in association with aortic stenosis or regurgitation, atherosclerosis, arteriolar hypertension, thyrotoxicosis—in essence, any cause for elevation in ventricular systolic pressure.

In the presence of an elevated peripheral resistance, where aortic diastolic pressure is 130 or more, regurgitation probably begins a fraction of a second before aortic outflow. Pressure in the ventricle usually rises so rapidly, however, that this consideration is of little practical importance.

Regurgitation is decreased when ventricular pressures are low. The peripheral resistance and bodily demands for blood are among the factors regulating the setting for aortic pressure and, because the heart is a self-regulatory pump, the level of intraventricular pressure. This is demonstrated in patient M. S. The total peripheral resistance was low-normal, and the intraventricular systolic mean pressure was only about 83 mm. Hg.

The systolic gradient was decreased in the presence of mitral stenosis or left ventricular failure, where the mean intra-atrial pressure was higher than normal. This was observed in patient E. L. In the studies following mitral valvuloplasty, the ventricular systolic pressure was 18 mm. Hg less than that preoperatively, but, because intra-atrial pressure had fallen 14 mm. Hg as a result of widening of the mitral valve, the regurgitant gradient was essentially unchanged.

Provided venous return is adequate, an increase in the systolic ejection period, as with tachycardia, would lead to an increased regurgitant blood flow and also to an increased aortic flow, and vice versa if this period were decreased.

Summary: The degree of regurgitation depends mainly on the cross-sectional area of the valvular defect and is of a large volume because it is being driven by systemic blood pressures of 100 to 150 mm. Hg into a region of relatively low pressure, the left atrium.

B. Mitral stenosis: With mitral regurgitation, the total left ventricular output naturally has to be greater than normal in order to maintain a normal aortic output. This was seen in patient M. S. who had pure mitral regurgitation without stenosis. On the other hand, in most of the patients with associated stenosis, the total left ventricular output was only slightly increased above normal, and the aortic output was decreased below normal.

The effect of mitral stenosis on blood flow is best understood by considering the orifice formula[17] solved for total left ventricular output (Fm):

$$MVA = \frac{Fm}{DFP \times 31 \sqrt{\text{"PC"} - 5}}$$

$$Fm = MVA \times DFP \times 31 \sqrt{\text{"PC"} - 5}$$

where MVA = stenotic mitral valve area in cm.^{2}
DFP = diastolic filling period in diastolic seconds per minute
31 = empirical constant
"PC" = pulmonary "capillary" pressure in mm. Hg
5 = assumed left ventricular diastolic pressure in mm. Hg.

As the valve area (MVA) decreases, the total left ventricular output must decrease unless pulmonary "capillary" pressure ("PC") rises or the diastolic filling period per minute (DFP) increases.

Pulmonary "capillary" pressure was observed to be moderately elevated and total left ventricular output slightly greater than normal. The level of pulmonary "capillary" pressure and the rate of valvular flow were almost the same in these patients as in those with pure stenosis of a similar degree (Tables II and III), indicating that the transvalvular pressure-flow equilibrium was mainly a result of the adaptation of the circulation to the degree of stenosis rather than to the regurgitation. The presence of regurgitation decreased the effective or aortic discharge, and when the presence of stenosis restricted total available inflow, regurgitation led to a subnormal aortic flow. The balance between pressure and flow tended to favor a safe pulmonary pressure level below colloid osmotic pressure, and, as stenosis increased, pulmonary pressure was maintained within a safe range at the expense of a decrease in total left ventricular inflow (Fig. 3). This may be seen if patients M. S. and E. L.$_2$ are compared. Both had similar pulmonary "capillary" pressures, but the inflow in patient M. S. was 1.9 L. per minute per square meter more than that of E. L.$_2$ because of the larger forward valve size in M. S. Thus, stenosis governed the available total left ventricular volume by leading to a balance between an increase in pulmonary "capillary"

pressure and how much the total left ventricular inflow may be increased. The regurgitant, aortic, and ventricular pressure-flow relationship determined how much of the blood escaped to the body and how much regurgitated. Stenosis, by limiting the *compensatory* increase in left ventricular stroke output, depressed aortic blood flow. The largest total left ventricular volumes were seen when both the stenotic mitral valve area and the regurgitant valve area were large, as in patients M. S., L. L., and A. D.$_2$ The demand for blood was high because of regurgitation, and the forward valve orifice was large enough that the demand could be met satisfactorily without major pulmonary pressure rises.

The total amount of left ventricular inflow in these patients was, on the average, about 1 L. per minute greater than that seen in patients with similar degrees of pure stenosis. Although the pressures and flow rates were similar, the duration of ventricular systole at a given heart rate was shorter in the patients with both mitral insufficiency and stenosis than in normal subjects or in those with pure stenosis (Fig. 4, Tables II and III). As a result, from five to ten seconds more were available each minute for diastole and ventricular inflow. There were two possible explanations for the shortened period of ventricular systole. (1) The double orifice and consequently greater ease of systolic discharge in mitral regurgitation might lead to a quickened ventricular systole. Feil and Forward,[43] however, found that the systolic periods in mitral insufficiency were well within normal limits, and hence the shortened period of ejection was not due to regurgitation per se. (2) All but one of the patients (F. K.) had auricular fibrillation, while none of the patients with pure mitral stenosis of similar degree was fibrillating. It has been shown[43,44] that ventricular systole is usually shortened in the presence of auricular fibrillation. Hence, auricular fibrillation aided in the circulatory adjustments to mitral regurgitation and stenosis by leaving more time available for diastole in every minute and therefore a greater volume of ventricular inflow per minute.

Summary: By restricting the total left ventricular inflow, mitral stenosis limited the ability of the left ventricle to compensate for the regurgitation. As a result, aortic output often was markedly decreased.

3. Total Pulmonary Resistance.—The calculation of total pulmonary resistance gives an index of the average daily pressure load against which the right ventricle must pump. It has been observed in other diseases[10,45] that there is a depression of stroke output as resistance increases, presumably due to strain on the right ventricle and the development of a new equilibrium between tissue blood flow demands and the optimum ability of the right ventricle to deliver blood.

In mitral regurgitation, the pulmonary pressure load consists of (a) elevation of pressure reflected from the left atrium due to (1) increased blood flow through the mitral valve due to regurgitation and (2) stenosis of the mitral valve, and (b) elevation of pressure required to drive blood through narrowed pulmonary arterioles. Right ventricular output bore an inverse logarithmic relationship to this resistance (Fig. 5). Blood flow was proportionately more decreased per unit of resistance in these patients than in patients with pure mitral stenosis apparently because of the numerous other factors in mitral regurgitation which

tend to depress cardiac output. This greater curtailment of output did not appear to be related to frank right ventricular failure because right atrial pressures were within the normal range in ten instances.

4. Factors Peripheral to the Left Ventricle Affecting Aortic Output.—The volume of blood discharged into the aorta depends on several factors. The blood is ejected through the aortic valve into a complex vascular network. Flow will depend on the ventricular pressure head, the size of the aortic valve orifice, and finally the resistance through the vascular system. One to 3 mm. Hg of pressure energy ordinarily are expended on velocity through the aortic valve orifice[17] unless aortic stenosis is present. When the aortic valve is stenotic, as with any obstruction to blood flow, there will result a rise in pressure head and decrease in blood flow. This is expressed as follows[17]:

$$CO = AVA \times SEP \times C \times 44.5\sqrt{LV_{sm} - A_{sm}}$$

where CO = aortic output in liters per minute
AVA = aortic valve area in cm.^{2}
LV_{sm} = left ventricular systolic mean pressure in mm. Hg
A_{sm} = aortic systolic mean pressure in mm. Hg
$44.5 = \sqrt{2g} = \sqrt{1960}$ = empirical constant
SEP = systolic ejection period in systolic seconds per minute
C = discharge coefficient.

Pressure is likewise utilized to overcome friction through the systemic vascular network. Blood flow varies with vascular resistance and pumping pressure according to the following formula:

$$CO = \frac{BA - 0}{R} \times 1332$$

where CO = aortic output in c.c. per second
BA = brachial arterial mean pressure in mm. Hg
R = peripheral resistance in dynes seconds cm.$^{-5}$
1332 = factor to convert mm. Hg to dynes per cm.^{2}

The lower the vascular resistance, the greater is the amount of blood pumped by a given amount of pressure energy; in a sense, systemic resistance acts like a brake or governor on the left ventricle. The total systemic resistance against which the left ventricle pumps is the sum of both aortic valve orifice and peripheral vascular resistances. The total systemic resistance competes with the "resistance" through the regurgitant mitral valve. While it is not valid to compare areas and resistances, the two are qualitatively similar in that large amounts of pressure are expended overcoming them. A small regurgitant area offers a high "resistance" to regurgitant flow because of the large pressure-to-velocity conversion at the small orifice which obstructs regurgitant flow. A high peripheral resistance dissipates pressure energy in overcoming friction which curtails peripheral flow. To decrease peripheral resistance, all other factors remaining unchanged, is, in effect, to increase the area or decrease the friction

of the peripheral vascular network. As a result, more blood will be discharged via the aorta at the same pressure head, the total ventricular output having increased (if venous return has increased proportionately) and the regurgitant volume remaining the same. The converse is also true. Therefore, alterations in peripheral resistance should be among the factors governing aortic cardiac output.

The interrelation of "resistances" in the systemic and regurgitant circuits and how they cause apportioning of blood flow are exceedingly complex because of the simultaneous interplay of other factors, such as venous return, left ventricular diastolic inflow, the pulmonary pressure level, and the self-regulation of ventricular pressure by the systemic resistance. In this particular study, the end result of proportionation was measured because aortic output was determined by the Fick method.

The amount of regurgitation in relation to aortic output depends in part on the duration of systolic ejection per minute. Except for minor differences, the duration of flow apparently affects aortic and regurgitant outflow in almost equal fashion. Regurgitation probably begins after the first few hundredths of a second of ventricular systole,[4] after ventricular pressures exceed atrial pressure, during which time diastolic inflow has been brought to a halt and flow reversed.[4] Within the next few hundredths of a second, ventricular pressure continues to rise to a level higher than that beyond the aortic valve, so that flow into the aorta under most conditions probably begins almost immediately after the onset of mitral regurgitation. Under conditions of severe tachycardia or diastolic hypertension, however, where aortic diastolic pressure is significantly elevated, there may be a more significant delay in the onset of aortic outflow and therefore a slight relative increase in the amount of regurgitant output. For the usual ranges of pulse seen, this should not be important.

Summary: The major factors peripheral to the left ventricle tending to decrease aortic output are aortic stenosis and increased peripheral vascular resistance.

5. *Myocardial Insufficiency.*—Myocardial weakness, such as may occur with active rheumatic carditis, may lead to ventricular failure with a rise in diastolic filling pressure and a fall in stroke output. The rise of diastolic pressure in the left ventricle and therefore left auricle diminishes the regurgitant pressure gradient across the mitral valve. This reduction is so slight, however, as to have little effect on the magnitude of the regurgitant flow because the regurgitation is proportional to the square root of this pressure gradient. In this small series of patients, only two (E. S. and D. N.) had evidence of significant right ventricular failure under basal conditions. It was not possible by the indirect techniques used here to define with certainty the status of the left ventricle.

In patients with mitral regurgitation and stenosis in whom aortic output is already depressed, a bad situation would be made worse by the presence of failure of either or both ventricles. As in mitral stenosis, when the left ventricle fails, the aortic output will diminish, and the pulmonary capillary pressure will rise, leading, in the extreme, to a shocklike state and pulmonary edema. When the right ventricle fails, the aortic output will fall farther, and peripheral rather than pulmonary congestion will appear.

The Interrelationship of Mitral Stenosis and Regurgitation

Because mitral insufficiency is almost invariably associated with mitral stenosis, their effects on one another must be considered briefly.

1. Effect of Stenosis on Regurgitation.—Mitral stenosis produces two effects on the dynamics of mitral insufficiency. The first is to reduce the available amount of blood entering the left ventricle through the mitral valve[10]; this in turn makes less blood available for ejection into the aorta. Because the regurgitant area is a fixed area, if ventricular pressures are normal, there is no reduction in the volume of regurgitation. The decrease in total inflow is directly borne by the aortic output which is decreased. In our patients, the aortic output was lower the more severe the associated mitral stenosis (Fig. 3).

The second effect of mitral stenosis is to raise the left atrial and pulmonary "capillary" pressures. Although this reduces the regurgitant pressure gradient between left ventricle and left auricle, the effect is rather slight in reducing the amount of regurgitation (1) because of the magnitude of the pressure gradient and (2) because flow is dependent on the square root of this pressure gradient. The most important contribution of mitral stenosis in this respect is the elevation of the pulmonary "capillary" pressure with the resultant tendency to pulmonary edema. The elevation of this pressure is almost entirely dependent on the degree of stenosis and only to the extent of 3 to 6 mm. Hg on the degree of regurgitation.

2. The Effects of Mitral Regurgitation on Mitral Stenosis.—When blood flows through the stenotic orifice, the kinetic load on the mitral valve has been observed to be the same or only somewhat increased in patients with associated insufficiency and stenosis as compared to patients with similar degrees of pure stenosis (Tables II and III). In other words, the amount of pressure in relation to the rate of blood flow through the mitral valve is not significantly different in these two groups. For example, patient J. D.[10] with pure mitral stenosis had a pulmonary "capillary" pressure of 19 mm. Hg and a valve flow rate of 303 c.c. per diastolic second through a 2.5 cm.^{2} valve. The hydraulics in patient A. D.$_2$, who had mitral stenosis and mitral insufficiency, were somewhat similar. Pulmonary "capillary" pressure was 26 mm. Hg, valve flow was 270 c.c. per diastolic second, and the area of the valve was 1.9 cm.^{2} However, the *effective* or aortic flow in A. D. was less than one-half that in J. D. In mitral insufficiency, therefore, for a given stenotic valve area, bodily blood flow frequently is markedly curtailed. In this group of patients with mitral insufficiency and mitral stenosis, none of whom had severe mitral stenosis, decrease of output was comparable to that seen in patients with pure mitral stenosis[10] whose stenotic valve areas were much smaller, i.e., less than 1.0 cm.^{2}

With a given degree of mitral stenosis, mitral regurgitation reduces aortic (and right ventricular) output (Fig. 3), and in the absence of left ventricular failure does not per se appreciably influence pressures in the pulmonary circuit or in the right ventricle. Unless left ventricular failure occurs as a result of severe mitral insufficiency, since flows are less and pressures the same, work of the right ventricle is less than that seen in patients with a similar degree of pure mitral stenosis.

When mitral stenosis and insufficiency are associated, each lesion tends to make the effects of the other lesion more severe. Clinically, for example, it has been observed that patients with mitral insufficiency are often severely incapacitated when the mitral valve stenotic area is as large as 1.5 cm.^{2} or more, while in pure mitral stenosis, major symptoms rarely occur until the valve is 1 cm.^{2} or less.[26] Similarly, none of our patients with mitral insufficiency had a valve less than 1 cm.^{2} in area while fully one-third of our patients with pure stenosis had areas of 0.5 cm.^{2} or less.[10] Large regurgitant areas were seldom seen unless the forward valve area was large, as in patient L. L. Patient E. L., who had moderate stenosis (1.1 cm.^{2}) and severe regurgitation (0.7 cm.^{2}) was in extremis up to the time of surgical widening of the valve.

The physiologic explanation for these facts is seen in Fig. 7, in which mitral regurgitant area is plotted against mitral stenotic area. This graph has been constructed assuming (1) different levels of aortic flow compatible with life and

THE OBLIGATORY INTERRELATIONSHIPS OF MITRAL STENOTIC AND REGURGITANT AREAS AND THEIR ADVERSE EFFECTS UPON ONE ANOTHER

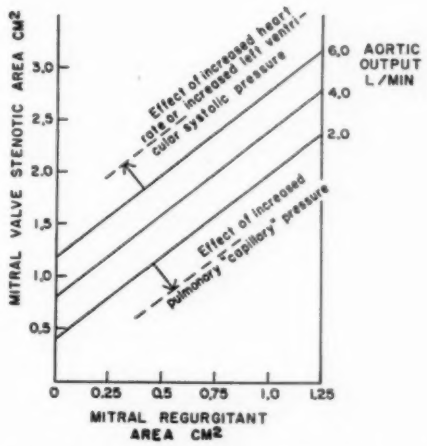


Fig. 7.—Mitral regurgitant area is plotted against mitral stenotic area. Assumed constants were (1) pulmonary "capillary" pressure at 25 mm. Hg, (2) left ventricular systolic mean pressure at 115 mm. Hg, and (3) pulse rate at 80. The requisite valve area relationships for different levels of aortic blood flow were then calculated.

As discussed in the text, the critical area for stenosis was 1.0 cm.^{2} and for regurgitation 1.0 cm.^{2}, whenever any degree of each lesion was associated. Certain effects pertinent to valvular surgery may be observed. If the stenosis is decreased while the regurgitant area remains unchanged, then aortic blood flow should be increased, other factors remaining constant, suggesting that mitral insufficiency is not a contraindication to surgery if there is stenosis present. Conversely, if regurgitation is decreased, while stenosis remains unchanged, aortic blood flow should be increased.

The effects of isolated alterations in other circulatory factors are illustrated by the broken lines which shift the solid aortic output curves to a new level. If pulmonary "capillary" pressure rises, more blood may flow to the periphery, but pulmonary edema may occur from the elevated pressure. If left ventricular systolic mean pressure increases, aortic cardiac output is decreased by preferential regurgitation due to the increased gradient of pressure. If pulse rate increases, there is less time for diastole and less blood will enter the left ventricle; if regurgitation is constant (as will occur if the pressure gradient is unchanged), the aortic output is decreased. Actually, all these factors are interacting, and seldom does a single change occur alone, but these effects are mentioned to indicate the directional effects of changes in pressure and flow times or aortic flow in the patient with mitral insufficiency and stenosis.

its demands, (2) an average resting pulmonary "capillary" pressure of 25 mm. Hg, (3) an average left ventricular systolic mean pressure of 115 mm. Hg, and (4) a resting pulse rate of 80. The chart is meant to convey an idea as to approximately what are the critical forward-regurgitant area relationships compatible with life.

If a patient had a stenosis of 1 cm.^{2}, then under these average conditions if the regurgitant area were greater than 0.5 cm.^{2}, aortic output would be critically reduced and the patient probably near death. Conversely, if a patient had a regurgitant area of 1 cm.^{2}, he probably could not survive unless the stenotic orifice had an area of 2 cm.^{2} or more. These observations are borne out by clinical findings mentioned earlier. When the two diseases are associated to any degree, the stenotic area probably will seldom be less than 1 cm.^{2} and the regurgitant area rarely more than 1 cm.^{2}

In summary, when the two diseases are associated, a progressive fall in left ventricular output occurs as the stenosis increases, and a progressive fall in aortic output occurs as the regurgitation area increases, while pressure in the left atrium and pulmonary circuit depends mainly on the degree of stenosis.

The Clinical Findings in Patients With Mitral Insufficiency and Stenosis

One of the major problems in clinical cardiology is the differential diagnosis between pure mitral stenosis and mitral insufficiency in association with stenosis. The clinical syndrome of mitral insufficiency has never been clearly defined and differentiated from that of mitral stenosis. This report has thus far described the altered physiology of mitral insufficiency and stenosis and indicated the differences between this and pure mitral stenosis. An attempt will be made to demonstrate certain differences between the clinical pictures of the two diseases and how, in part, this is explicable in terms of their respective physiologic patterns.

Most of our patients with regurgitation had mild mitral stenosis, yet in contrast to patients with similar degrees of pure stenosis, all of them were incapacitated by symptoms. Neither group had dyspnea as a prominent symptom. This symptom was probably a function of the degree of the mitral stenosis, which so intimately affects the level of pressure in the pulmonary circuit. The major symptom in all the patients with mitral insufficiency was that of *fatigue*, tiredness, and weakness, and in over one-half this was information volunteered by the patient as a primary complaint. In only one of the patients with pure mitral stenosis of similar degree was this symptom prominent. The presence of fatigue on the slightest effort was probably related to the extremely low aortic cardiac output and poor tissue blood flow seen in so many of these patients.

Dyspnea was not a prominent symptom in either group of patients. This study includes only patients with mild to moderate degrees of regurgitation, where regurgitant blood flow did not exceed the aortic blood flow by more than 50 per cent. If the regurgitation were so marked that severe left ventricular failure resulted from the enormous flow load, then dyspnea, orthopnea, and cough would probably appear.

Symptoms of right ventricular failure, namely chronically enlarged liver and chronic peripheral edema, were notably absent in almost all the patients with

mitral regurgitation. This would seem to fit with the observed physiologic facts that the right ventricular diastolic filling pressure is often within normal limits and that regurgitation decreases the load on the right ventricle.

TABLE V. SUMMARY OF CLINICAL FINDINGS IN PATIENTS WITH MITRAL VALVULAR DISEASE

	ELEVEN PATIENTS WITH MITRAL REGURGITATION AND STENOSIS		SEVEN PATIENTS WITH COMPARABLE PURE MITRAL STENOSIS[26]		TWENTY-THREE PATIENTS WITH SEVERE PURE MITRAL STENOSIS[26]	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Severity of dyspnea						
None	0	0	1	14	0	0
1+	2	18	4	57	0	0
2+	9	82	0	0	5	22
3+	0	0	1	14	6	26
4+	0	0	1	14	12	52
Paroxysmal nocturnal dyspnea	4	36	2	29	14	61
Hemoptysis	1	9	2	29	4	17
Fatigue	10	100*	1	14	4	17
Hepatomegaly (2+ or more)	1	10*	0	0	12	52
Edema (2+ or more)	1	10*	0	0	11	48
Auricular fibrillation	10	91	0	0	9	39
Left atrium by fluoroscopy						
Dilatation (2+ or more)	11	100	3	43	22	96
Paradoxical pulsation	7	64	2	29	4	17
Ventricular hypertrophy by electrocardiogram						
Right	4	40*	2	29	18	78
Left	3	27	0	0	0	0

*Total of ten valid observations of this clinical finding.

All patients had an apical systolic murmur, but this finding was not specific because 40 per cent of patients with pure stenosis had apical systolic murmurs of Grade 2 or more. In ten of the twelve patients with mitral insufficiency and stenosis, however, this murmur was of Grade 3 intensity or more, while this was observed in only 17 per cent of patients with pure mitral stenosis.[26] Thus, while the absence of a systolic murmur probably excluded regurgitation,† the presence

†Since this paper was submitted for publication, five patients without apical systolic murmurs were found to have significant regurgitation at the time of mitral valvuloplasty.

of one was by no means diagnostic, although the greater the intensity of the murmur, the more likely it was to be indicative of insufficiency. There was a rough correlation between the grade of murmur and the volume of regurgitated blood. The interpretation of the apical systolic murmur was further complicated by (1) the not infrequent presence of tricuspid regurgitation which in itself can sometimes produce an apical systolic murmur and simulate mitral regurgitation and (2) the probability that some systolic murmurs are not in any way due to valvular regurgitation.

In striking contrast to patients with the same degree of pure stenosis, patients with regurgitation had moderately to markedly enlarged left atria. All but one of the patients with insufficiency and stenosis and large left atria were fibrillating, while all of those with mild pure stenosis had small left atria and normal sinus rhythm. What the relationship was, if any, between atrial size and rhythm could not be determined, nor was it apparent whether atrial dilatation was a result of the high swinging pressures seen in regurgitation, of the duration of pressure elevation, or of auricular myocardial disease.

Systolic pulsation of the left auricle has been described for many years in mitral regurgitation[46] and is a visual reflection of volume increase in the left auricle during ventricular systole. It is dependent upon (1) the initial size of the left auricle in relation to volume increase, (2) the volume of regurgitation, and (3) the volume of pulmonary venous inflow. Thus, the presence or absence of pulsation is not necessarily diagnostic of mitral regurgitation. Over one-half of our patients had paradoxically pulsatile left atria, while two of seven patients with mild pure stenosis had what was reported as pulsatile left atria.

The electrocardiogram revealed right ventricular hypertrophy in five of the twelve patients, one of whom had had severe pure mitral stenosis and right ventricular hypertrophy present prior to mitral valvuloplasty (E. D.), while this was present in two of seven patients with mild pure stenosis. The majority of patients did not have left ventricular hypertrophy, but when present and not due to other causes, it was almost diagnostic and usually indicative of a high degree of regurgitation (L. L., E. L., and A. $D._2$). Left and right ventricular hypertrophy were combined in two patients and totally absent in six others.

In summary, the clinical syndrome of mitral regurgitation as deduced from the preceding analysis includes limitation of activity by excessive *fatigability* and tiredness, severe dyspnea only when left ventricular failure is present from severe regurgitation or when associated mitral stenosis is moderately severe (1.0 to 1.5 $cm.^2$ in area), the frequent absence of hepatomegaly and edema, an apical systolic murmur, auricular fibrillation, an invariably enlarged left atrium by fluoroscopy which often exhibits paradoxical pulsation, and the not uncommon absence of any ventricular preponderance by electrocardiogram. When left ventricular hypertrophy was present, it usually indicated severe regurgitation. The louder apical systolic murmurs were suggestive but not diagnostic of mitral regurgitation.

The clinical detection of mitral regurgitation in the presence of stenosis is at best difficult. They can readily be separated from patients with mild pure

stenosis on the basis of clinical symptoms and fluoroscopy of the heart alone, but their differentiation from patients with pure severe mitral stenosis is often impossible.

Patients with severe mitral stenosis tend to have, or have had in the past, more dyspnea, orthopnea, and hemoptysis, and hepatomegaly, edema, and right ventricular hypertrophy are much more frequent.[26] These patients undoubtedly would complain of fatigue on exertion as do patients with associated regurgitation, but dyspnea is usually so severe and so alarming as to overshadow all other exertional complaints. A small group of the patients with pure severe stenosis and associated pulmonary vascular disease do have easy fatigability, tiredness, and weakness as prominent symptoms, and this may be mistaken for mitral insufficiency. These patients, however, usually have had a past history of severe dyspnea and orthopnea which gradually disappeared over the years as the pulmonary vascular lesion developed, more evidence for right ventricular failure clinically, and, almost invariably, right ventricular hypertrophy electrocardiographically.[26]

The electrocardiographic findings are often very helpful because either significant stenosis or significant regurgitation results in univentricular hypertrophy. The absence of right ventricular hypertrophy or the presence of combined hypertrophy in a patient with disability believed due to mitral disease suggests the presence of both mitral regurgitation and stenosis. Left ventricular hypertrophy probably indicates a mild stenosis and a severe degree of regurgitation, as judged from our cases.

In summary, mitral regurgitation can be suspected in the presence of stenosis from a history of more fatigue and less dyspnea, in the absence of major peripheral congestive phenomena, in the presence of a pulsating left atrium, and from the type of ventricular hypertrophy by electrocardiogram.

CONCLUSIONS

1. One patient with pure mitral regurgitation and eleven patients with both mitral regurgitation and stenosis were studied by the technique of cardiac catheterization. The forward area of the mitral valve was known in seven patients. With this information, it was possible, in these seven patients, to analyze the dynamics of the left side of the heart by means of hydraulic principles.

2. In one case of pure mitral regurgitation, the aortic output was found to be normal and total left ventricular output and pressure work to be increased. Pressures in the pulmonary circuit were relatively unaffected.

3. In the patients with both mitral regurgitation and stenosis, (a) the aortic output was found to be markedly decreased below normal and the total left ventricular output somewhat increased above normal. Regurgitant blood flow on the average equalled aortic blood flow and therefore constituted one-half the total left ventricular discharge. (b) Left ventricular pressure work was somewhat increased. (c) Pulmonary "capillary" pressure was moderately elevated and the V wave increased in height. (d) The pressure-flow equilibrium across the stenotic mitral valve in these patients was the same as that seen in patients

with the same degree of pure mitral stenosis. (e) Pulmonary arteriolar resistance was found to be only somewhat increased. (f) Right ventricular pressure work, on the average, was within normal limits because of the low output and the small increases in pulmonary resistance. (g) Right ventricular failure, as judged by an elevated right atrial mean pressure, was not commonly seen in these patients.

4. Left ventricular hypertrophy by electrocardiogram was seen in only 27 per cent of the patients and generally in those with the largest total left ventricular outputs. Right ventricular hypertrophy was likewise seen in only 45 per cent of the patients, usually in those with the highest total pulmonary resistance, and only on three occasions was this univentricular hypertrophy.

5. The regulation of aortic blood flow in the presence of mitral regurgitation depended on: (a) the left ventricular volume and stroke capacity, (b) the degree of mitral regurgitation and the degree of mitral stenosis, (c) the height of the total pulmonary resistance, (d) the presence of aortic stenosis and the level of systemic vascular resistance, and (e) myocardial incompetency.

6. The effects of stenosis and regurgitation may be summarized as follows: Stenosis tends to restrict available left ventricular stroke volume and to elevate pulmonary pressures, while regurgitation tends to limit the aortic output for a given degree of stenosis.

7. The clinical syndrome of mitral regurgitation and stenosis has been described. Easy fatigability was found to be the commonest and most prominent complaint and usually overshadowed the moderate degree of dyspnea present. Signs of right ventricular failure were infrequently seen. A loud apical systolic murmur was consistent with, but not diagnostic of, mitral regurgitation. A greatly enlarged, often paradoxically pulsating, left auricle was seen in the majority of patients. Univentricular hypertrophy by electrocardiogram was often absent.

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THE RESPONSE OF THE PERIPHERAL VENOUS PRESSURE TO EXERCISE IN CONGESTIVE HEART FAILURE

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THE clinical function tests in general use for determining the presence of congestive heart failure include estimation of the peripheral venous pressure at rest and measurement of various circulation times. Quite frequently these tests do not give definitive results when the congestive heart failure is mild and where diagnostic assistance is needed, whereas positive results are the rule in patients with severe congestive failure where the additional information is not essential to establish the hemodynamic status. A need exists for a simple test which would detect the milder degrees of congestive heart failure.

Experimental evidence suggests that an abnormal increase in venous pressure during exercise might be a more sensitive index of early congestive heart failure than the venous pressure at rest. Following acute ligation of a coronary artery, the venous pressure in the anesthetized dog remained normal at rest but became abnormally elevated when the limbs were exercised.[1]

Clinical studies on the value of the response of the peripheral venous pressure to exercise have yielded varying results. White, Barker, and Allen[2] studied seven patients with congestive heart failure of varying degrees of severity and concluded that the elevation in venous pressure during exercise was not a good index of the severity of heart failure. Harrison, Harrison, Calhoun, and Marsh[3] reported that the rise in venous pressure during exercise was proportionate to the degree of congestive heart failure. In fifty-four patients with heart failure, Szekely[4] found sixteen patients who had normal venous pressures at rest, and twelve of these showed abnormal elevations in the pressure during exercise. Nieuwenhuizen[5] reported that in patients with heart disease a normal resting venous pressure is sometimes associated with an abnormal rise in the pressure during exercise.

Because the clinical studies thus far have not been entirely definitive, an evaluation of the venous pressure response to exercise was undertaken.

METHOD

Venous pressure was measured in an antecubital vein with a saline manometer. The subjects were supine, and when orthopneic the head was elevated

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30 to 40 degrees. The zero reference level was 5 to 6 cm. posterior to the angle of Louis. After the patients had rested for about fifteen minutes, a No. 18 or No. 19 gauge needle was inserted into an antecubital vein, and pressures were recorded every minute until they had stabilized (usually fifteen minutes). Exercise was then begun; it consisted of flexing one leg completely thirty times a minute for two minutes. The leg was moved so that the heel was just above and parallel with the mattress and did not drag on it. Venous pressure was recorded every half minute during exercise, every half minute for the first three minutes after the end of the exercise, and every minute thereafter until the pressure returned to the range of the control values. The test was then almost always repeated, and the results of the two tests were averaged.

RESULTS

Data were derived from 102 tests on twenty-seven patients with varying degrees of congestive heart failure, twelve tests on twelve patients with pulmonary disease, and twenty tests on twenty patients without either cardiac or pulmonary disease. The patients with pulmonary disease had varying degrees of dyspnea but no clinical evidence of heart disease. The patients with heart failure were classified as mild, moderate, or severe according to the degree of peripheral edema, enlargement of the liver, engorgement of the peripheral veins, orthopnea, pulmonary râles, and exertional dyspnea.

The upper limit of normal for the venous pressure at rest, and during exercise, was determined by statistical analysis of the data. The mean values and standard deviations are given in Table I under the column "Control Patients." The upper limits of normal, taken as 2σ above the mean pressures, were as follows: resting venous pressure, 85 mm. of water; rise in venous pressure during exercise, 60 mm. of water.

TABLE I. VENOUS PRESSURES IN PATIENTS WITH PULMONARY DISEASE AND COMPENSATED HEART DISEASE COMPARED WITH PATIENTS WITHOUT CARDIAC OR PULMONARY DISEASE

	PATIENTS WITH PULMONARY DISEASE		P	CONTROL PATIENTS		P	PATIENTS WITH HEART DISEASE WITHOUT CONGESTIVE HEART FAILURE	
	MEAN	σ		MEAN	σ		MEAN	σ
Venous pressure at rest (mm. H_2O)	28	24	0.05	45	19	0.40	50	23
Rise in venous pressure during exercise (mm. H_2O)	26	16	0.40	21	20	0.02	35	18
Number of patients	12			20			25	

Each P value refers to the data for the groups on either side of it and was derived from Fisher's table of t values.

The data for the patients with pulmonary disease indicate that these patients probably had a significantly lower venous pressure at rest than the control patients

(Table I). However, there was no significant difference in the rise in venous pressure during exercise in the two groups.

The data for those patients who had previously had congestive heart failure, but were compensated at the time of study, indicate resting venous pressures which are not significantly different from the values for the control group (Table I). However, the patients with compensated heart disease probably had a slightly greater response to exercise than the control patients.

An analysis of the resting venous pressure and the venous pressure response to exercise in patients with varying degrees of congestive heart failure is presented in Table II. With one exception, the venous pressure, both at rest and during exercise, increased significantly with increasing severity of heart failure. (The difference between the rise in venous pressure during exercise in mild and moderate congestive failure is not significant.)

TABLE II. THE RESTING VENOUS PRESSURE AND THE RISE IN VENOUS PRESSURE DURING EXERCISE IN VARYING DEGREES OF HEART FAILURE

	DEGREE OF CONGESTIVE HEART FAILURE										
	ABSENT		P	MILD		P	MODERATE		P	SEVERE	
	MEAN	σ		MEAN	σ		MEAN	σ		MEAN	σ
Resting venous pressure (mm. H_2O)	50	23	<0.01	100	49	<0.01	149	53	0.02	181	41
Rise in venous pressure during exercise (mm. H_2O)	35	18	<0.01	78	44	0.1	94	29	0.02	121	39
Number of tests	25			26			35			16	

Each P value refers to the data for the groups on either side of it and was derived from Fisher's table of *t* values.

Serial determinations were made on six patients as they recovered from severe congestive heart failure. Their data (Fig. 1), in general, show the same result as those in Table II, a progressive decrease in the resting venous pressure and a smaller rise in venous pressure during exercise as the severity of the heart failure decreased. The data also illustrate the usefulness of determining the venous pressure response during exercise. In four of the six patients, the rise in venous pressure during exercise was abnormally increased at a time when the resting venous pressure had fallen into the normal range.

The analysis in Table III was made in order to determine whether the rise in venous pressure with exercise can be used to diagnose the milder degrees of congestive heart failure and, in particular, failure of such mild degree that the resting venous pressure is still within the normal range. The table shows that, in patients with mild congestive heart failure, 50 per cent of the determinations of resting venous pressure were abnormally high, whereas 73 per cent of the determinations of the venous pressure response to exercise were abnormally

increased. In patients in moderate and severe congestive heart failure, 90 per cent of the determinations of resting venous pressure and 94 per cent of the measurements of the venous pressure response during exercise were abnormally elevated. In only one of the 102 determinations on patients with heart disease was there an abnormally high resting venous pressure with a normal rise in pressure during exercise.

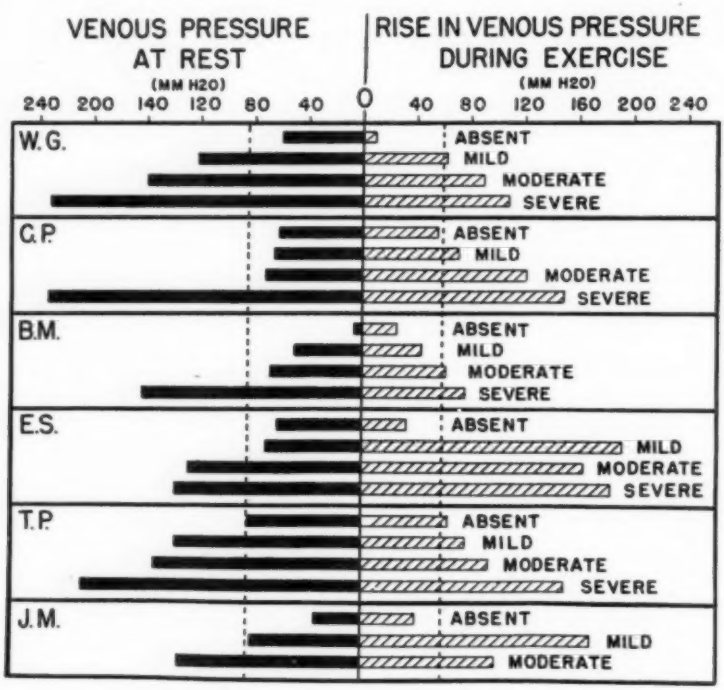

Fig. 1.—Venous pressure at rest and the rise in venous pressure during exercise in varying degrees of congestive heart failure in six patients as they recovered cardiac compensation.

"Absent," "mild," "moderate," and "severe" refer to the degree of congestive failure. The dotted vertical lines indicate the upper limits of normal for venous pressure at rest and for the rise in venous pressure during exercise.

DISCUSSION

In considering the type of exercise to be used, it was felt that the performance of a standard amount of work would not insure a uniform energy expenditure, since the energy expenditure could vary with the manner in which the work was done. It was decided that, by having the patient flex the leg, a stress would be imposed which was most suitable for the patient's muscular development, would not require skill, and would keep the apparatus for the test at a minimum.

The clinical classification of the cardiac patients into grades of severity of congestive failure is crude but probably sufficiently accurate for a study of this type, particularly since this evaluation of all patients was done by the same person, without knowledge of the results of the exercise tests.

The progressively higher venous pressures at rest and during exercise as the severity of the congestive heart failure increased substantiate the results pre-

viously reported.[3] However, the data for individual patients studied at varying stages of heart failure show that these trends are only general and do not correlate strictly with the clinical course of the patient.

TABLE III. A COMPARISON OF THE INCIDENCE OF ABNORMAL VENOUS PRESSURE (AT REST AND DURING EXERCISE) IN MILD CONGESTIVE HEART FAILURE AND IN MODERATE AND SEVERE CONGESTIVE HEART FAILURE

	MILD CONGESTIVE HEART FAILURE	MODERATE AND SEVERE CONGESTIVE HEART FAILURE
Total number of tests	26	51
Number of tests with an abnormal venous pressure at rest	13 (50%)	46 (90%)
Number of tests with an abnormal venous pressure rise during exercise	19 (73%)	48 (94%)

The significantly lower resting venous pressures in the patients with pulmonary disease than in the control patients may be due to an error in the positioning of the zero reference level of the manometer in these patients. Since the chests were often emphysematous and abnormally thick, 5 to 6 cm. posterior to the angle of Louis would tend to be higher than the mid-point of the right atrium, and consequently the pressures would be erroneously lower. The normal rise in venous pressure during exercise in patients with pulmonary disease, in contrast to the abnormal rise in patients with heart failure, has proved useful in the clinical differentiation between dyspnea due to cardiac and that due to pulmonary disease, particularly when the resting venous pressure approached the upper limit of normal.

The venous pressure response to exercise proved to be a somewhat more sensitive, and helpful, index of mild congestive heart failure. Thus, in patients considered to have this degree of failure, 73 per cent of the exercise tests gave abnormally increased rises in venous pressure during the exercise, whereas only 50 per cent of the measurements of resting venous pressure were abnormally high. Since most of the patients with the more severe grades of congestive heart failure had abnormally high venous pressures at rest, the venous pressure response to exercise was, therefore, of little further value.

SUMMARY

1. The resting venous pressure and the rise in venous pressure during exercise were determined in twenty-seven patients with heart disease of varying degrees of severity, in twelve patients with pulmonary disease, and in twenty patients without cardiac or pulmonary disease.

2. In general, both the resting venous pressure and the rise in venous pressure during exercise increased with the severity of the congestive heart failure.

3. In patients with mild congestive failure, one-half of the determinations of venous pressure at rest were abnormally high, whereas approximately three-fourths of the determinations of the rise in venous pressure during exercise were

abnormally increased. Almost all the patients with more severe congestive heart failure had both an elevated venous pressure at rest and an abnormally increased rise in pressure during exercise. The venous pressure response to exercise is, therefore, a somewhat more sensitive index of the milder degrees of congestive heart failure than the venous pressure at rest; in severe congestive failure it offers no advantage.

The authors wish to thank Mr. William H. Becker for his helpful assistance in this study.

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CONSTRICTIVE PERICARDITIS CAUSED BY SOLITARY METASTATIC CARCINOSIS OF THE PERICARDIUM AND COMPLICATED BY RADIATION FIBROSIS OF THE MEDIASTINUM

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CARCINOMATOUS involvement of the pericardium as part of widespread metastatic disease is not frequent.[1-7] Constrictive pericarditis produced by such pericardial infiltration during the clinical course of metastatic carcinosis is very infrequent.[8,9] Isolated metastatic carcinoma of the pericardium without other metastases is extremely rare.[2] Solitary diffuse metastatic carcinoma of the pericardium producing solely and primarily the clinical picture of chronic constrictive pericarditis has not been reported. In their study of constrictive pericarditis, Andrews, Pickering, and Sellors[10] dismissed metastatic carcinoma as an etiological factor. The features of this presentation are not only noteworthy because of their rarity, but are instructive because of the sequence of the clinical events and the complicating factor of radiation fibrosis.

CASE REPORT

The patient, a 52-year-old white woman, was admitted to the Jewish Sanitarium and Hospital for Chronic Diseases because of intractable edema of two and one-half months' duration. Fourteen years before admission, a left radical mastectomy had been performed for duct carcinoma of the breast, grade II (Fig. 1). There were no lymph node metastases. Postoperative edema of the left arm gradually cleared. X-ray therapy was administered to the left parasternal area and to the left axilla. A cough began soon after radiation therapy was completed and was attributed to pulmonary fibrosis of the left upper lobe. The cough continued and was productive of a small amount of white mucoid sputum. Excision of a right ovarian cyst had been performed eight years before admission. One year before admission, a benign neoplasm had been excised from the right breast. There was no history of active tuberculosis, rheumatic fever, or sepsis.

Aside from the chronic persistent cough, and the operations mentioned, the patient had been well for fourteen years. Four months before admission to the hospital, she was seen by one of us because of increasing dyspnea and a feeling of pressure in the upper abdomen of seven months' duration. Palpitation after marked exertion was troublesome. However, there was no orthopnea or cyanosis. There was no history of any of the usual causes of heart disease. At that time, physical examination revealed the patient to be chronically ill, but not dyspneic. She weighed 151.5 pounds. The eyelids were slightly edematous. The trachea was freely moveable. There was moderate edema of the left upper extremity. The neck veins were distended. The heart was not enlarged. The ventricular and pulse rates were 132 per minute and regular. The blood pressure was 140/90 mm. Hg. There were fine, moist râles over both lower lung fields posteriorly,

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and there was dullness over the left upper lobe. The liver edge was felt 4 fingerbreadths below the right costal margin. Ascites was present. There was marked pitting edema of the lower extremities.

Urinalysis showed no abnormality. The electrocardiogram, taken in September, 1950 (Fig. 2), showed a regular sinus rhythm of 125 per minute. By fluoroscopic examination, the heart was displaced but not enlarged. There was considerable fibrosis of the upper lobe of the left lung. Fluid was present at both lung bases.

Digitalization and mercurial diuretics were effective in reducing the weight from 151.5 pounds to 129.0 pounds. However, the liver was still enlarged to 4 fingerbreadths below the right costal margin. The venous pressure was 18.5 cm. of water, and the Decholin circulation time was 30 seconds. Despite continued therapy, peripheral edema and ascites persisted. The diagnosis of constrictive pericarditis was suspected, and the patient was hospitalized for possible surgical intervention.

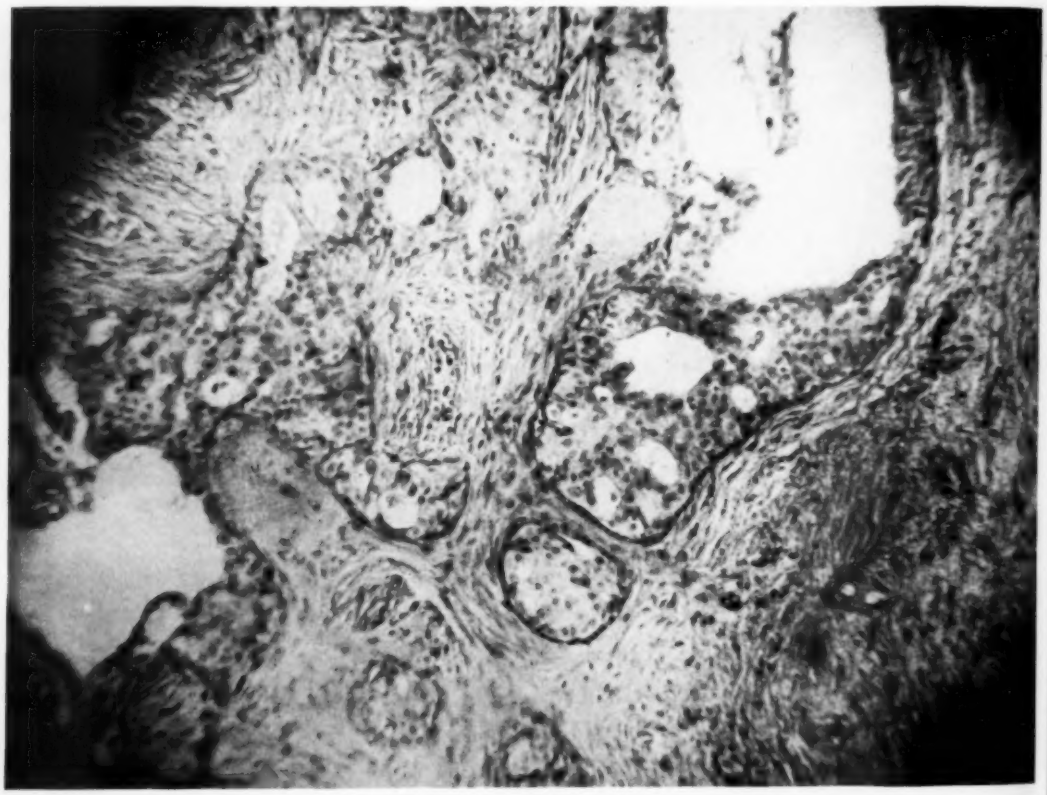

Fig. 1.—Section of breast tissue: Intraductal mammary carcinoma, grade II. (×260.)

When admitted on Oct. 13, 1950, the patient was dyspneic at rest. She was seized with paroxysms of coughing upon assuming the recumbent position. The cough was productive of white mucoid sputum. There was no cyanosis or clubbing. The sclerae were slightly icteric. The neck veins were distended even when the patient was in the sitting position. The tongue veins were prominent. A well-healed left radical mastectomy scar was present. Over the sternum and precordium, the skin was thickened and adherent to the underlying thoracic cage. There were some brown pigmentation and telangiectasia in this area due to previous radiotherapy. The trachea was not deviated or fixed. A tracheal tug was absent. There were marked dullness, bronchial breathing, and bronchophony over the left upper lobe anteriorly and posteriorly. There

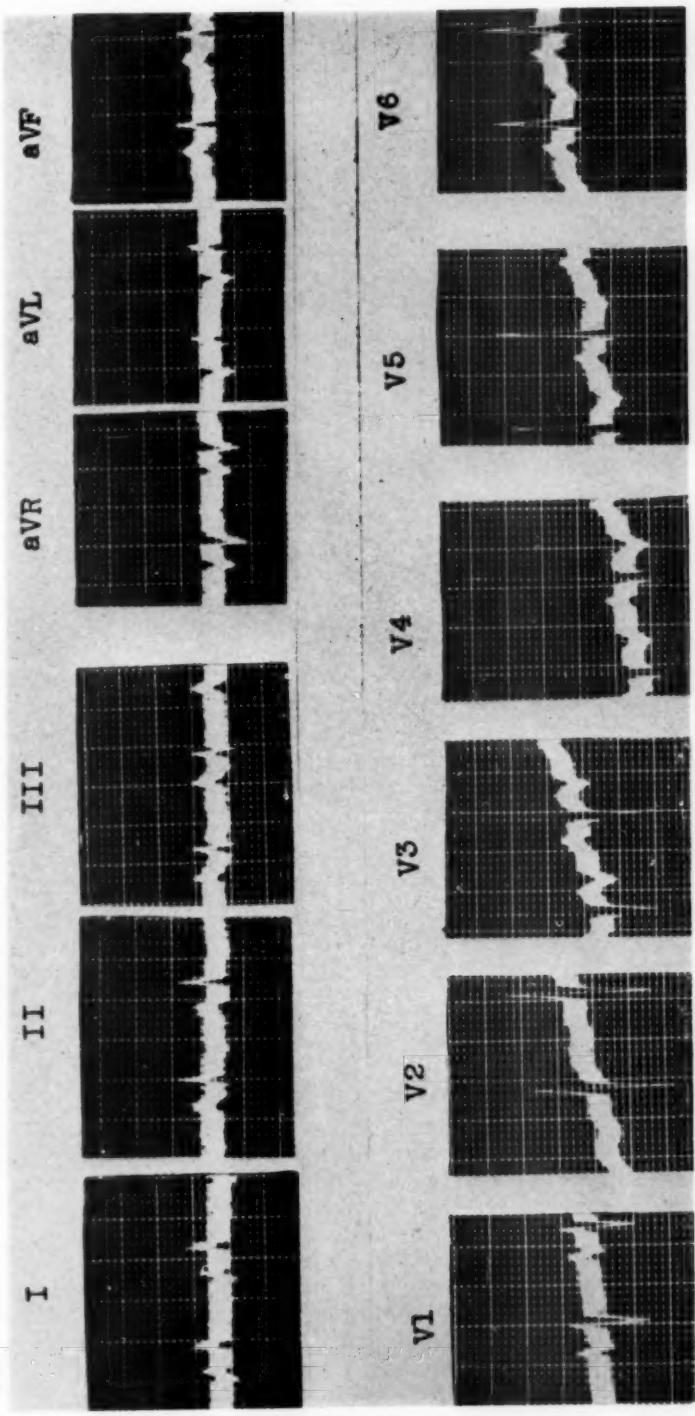

Fig. 2.—Electrocardiogram taken in September, 1950: Note the low voltage in the standard and extremity leads. The P waves are prominent and show intrinsicoid deflections. The T waves are either flat or inverted. The RS-T segments are not significantly displaced.

were dullness, bronchovesicular breathing, and egophony at the right lung base posteriorly and at the lower left axilla. Many musical râles were heard during expiration.

There was visible pulsation of the heart at the fourth intercostal space at the left sternal border, and there was inspiratory retraction at the fifth intercostal space at the left mid-clavicular line. The heart was not enlarged. The heart sounds were good. There were no murmurs. Sinus tachycardia at the rate of 150 per minute was present. The blood pressure was 128/90 mm. Hg. There was pitting edema of the lower abdominal wall and lower back. The abdomen was distended with ascites. A firm liver edge was felt at the umbilicus. The spleen was not felt. Marked pitting edema of both lower extremities was present. There was pitting edema of the left upper extremity, while the right upper extremity was not edematous. The amplitude of the radial pulse was low and became almost imperceptible with deep inspiration, the so-called "pulsus paradoxus" (Fig. 3).

By fluoroscopic examination, the right lung field was emphysematous. Fluid obliterated the right costophrenic sinus. The left lung field showed fibrosis and collapse of the left upper lobe and increased aeration of the left lower lobe. The area of increased aeration seemed to be completely surrounded by a curved density with a sharp border, interpreted as a fibrous thickening of the pleuropericardial junction. An adhesion extended from the left leaf of the diaphragm to the left hilum. In this region, the diaphragm was fixed and tented. Diaphragmatic excursions were shallow. The heart itself did not appear enlarged, and its borders were difficult to delineate because of dense adhesions. Cardiac pulsations were small. This was confirmed by a kymogram taken on Oct. 24, 1950.

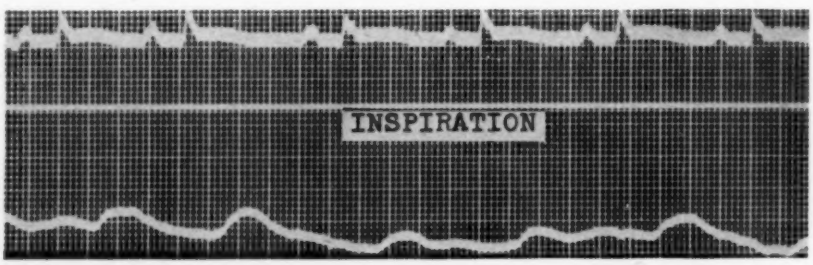

Fig. 3.—The radial pulse amplitude is low. Note the further decrease in amplitude with deep inspiration.

A roentgenogram of the chest taken on Oct. 16, 1950 (Fig. 4) confirmed the fluoroscopic findings. There was increased density of the left costophrenic sinus, which proved to be a pleural effusion by pleural tap. Overlying the heart and just to the left of the spine, there was a sharp-edged density which extended from the left clavicle to the left side of the dighragm. This density was clearly demonstrated in an overexposed Bucky film of the chest. The trachea and bronchi were not displaced. The heart did not appear enlarged. Its contour was distorted and pulled slightly upward and to the left.

Radiographic examination of the spine and long bones failed to reveal metastases.

The hemoglobin was 14.0 Gm. per 100 c.c. of blood; the red blood cell count was 5.4 million. The white blood cell count was 5,800 of which 68 per cent were segmented forms, 26 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. The Mazzini test was negative. Urinalysis consistently showed 3 plus albumin, 2 to 3 white blood cells, and an occasional red blood cell and granular cast per high-power field. There was never any bile in the urine. The specific gravity of random samples varied from 1.011 to 1.021. The sedimentation rate was 5 mm. per hour (Wintrobe). There were no tubercle bacilli in the sputum or in the gastric juice. The blood sugar and urea nitrogen were 117 and 20 mg. per cent, respectively. The total protein was 7.0 Gm. per cent of which 4.1 Gm. were albumin and 2.9 Gm. globulin. One month later, the total protein was 7.0 Gm. per cent of which 3.3 Gm. were albumin and 3.7 Gm. globulin. The blood sodium was 142 meq., the potassium 3.8 meq., and the chloride 91 meq. per liter. The calcium was 9.2 mg. and the phosphorus 3.4 mg. per cent. The blood acid phosphatase was 2.6 and the alkaline phosphatase 12.3 King-Armstrong units. The thymol turbidity was 2.9 units

(normal 0 to 4.5 units), and the cephalin flocculation was negative. The blood cholesterol was 192.5 mg. per cent of which 70 per cent of 133 mg. was esterified. The bilirubin was 6.2 mg. per cent of which 3.9 mg. were direct acting.

An electrocardiogram taken in November, 1950 (Fig. 5) showed lower voltage of the QRS complexes. Compared to the record of September, 1950, there were now RS-T elevations in the standard leads, aV_F, and V_2 to V_7. The T waves were still abnormal but were no longer inverted in V_2 to V_6.

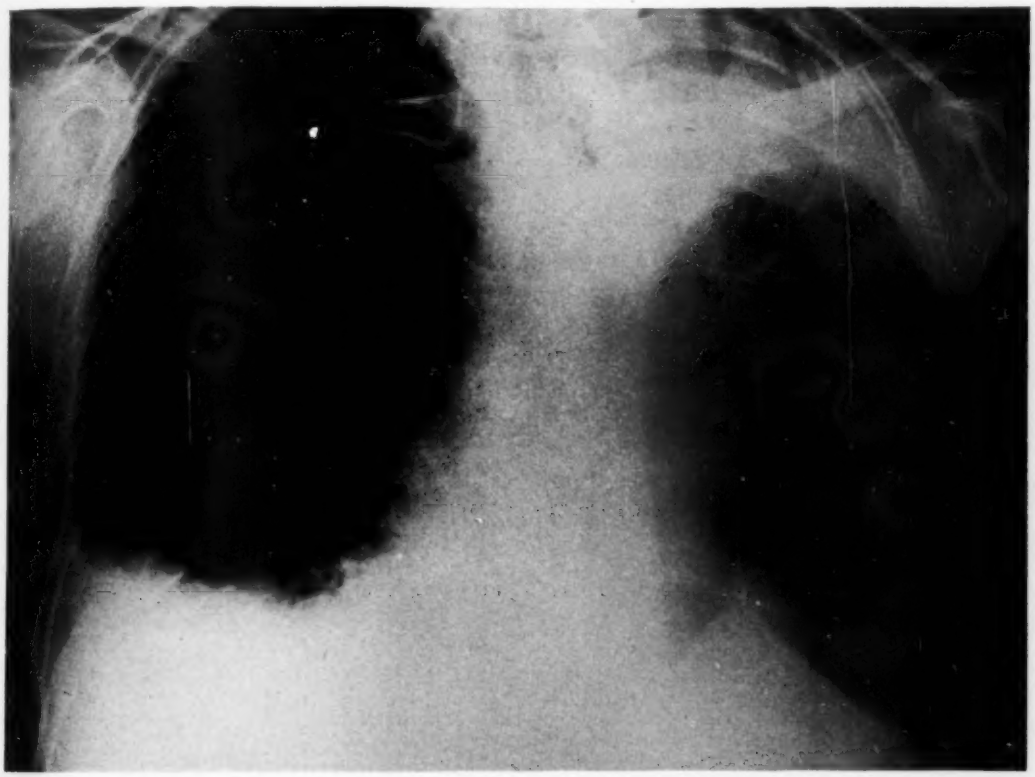

Fig. 4.—Roentgenogram of the chest, October, 1950: Note the fibrosis of the left upper lobe with pulling of the superior mediastinum to the left. The sharp-edged density overlying the heart near the spine and the triangular adhesion at the left diaphragm are clearly demonstrated. The right pleural effusion is distinct. (The print has been overexposed in order to delineate more clearly the fibrous adhesions.)

Course.—The entire course of the illness was afebrile. An attempt was made by the use of digitalis, mercurial diuretics, and a salt-free diet to reduce the anasarca and to improve the vital capacity. On Oct. 20, 1951, 800 c.c. of clear yellow fluid were aspirated from the right pleural cavity. No tumor cells or tubercle bacilli were found. The fluid was a transudate with seven white blood cells per cubic millimeter, a specific gravity of 1.012, and a protein content of 2.2 Gm. per cent. Within two weeks, it became clear that diet, diuretics, and digitalis were ineffective. The venous pressure was 47.4 cm. of water. The ether time was 22 seconds and the Decholin time 30 seconds. After the patient took mercurial diuretics for another week, the weight remained at 140 pounds. The venous pressure was 42.0 cm. of water. The ether time was 26.0 seconds and the Decholin time 34 seconds. The pulse pressure was small, blood pressures of 130 mm. systolic and 100 mm. diastolic being recorded.

The patient was troubled by increasing dyspnea and cough. The recumbent position would induce paroxysms of coughing productive of white mucoid sputum. Edema increased despite

therapy, and the inordinate degree of edema of the left upper extremity was remarkable. The sputum became blood streaked although there was neither localized chest pain nor fever. After a fair trial of medical therapy had failed to improve the patient's condition, surgical intervention was attempted, despite the poor risk. The presumptive diagnosis was constrictive pericarditis. It was also recognized that radiation fibrosis of the mediastinum and lung complicated the clinical picture.

Surgical Exploration.—A reversed, J-shaped incision was made along the left parasternal area from the third to the sixth costal cartilages, and then laterally. The left breast and most of the muscles of the chest wall were absent. The anterior surface of the cartilages was covered with fibrous tissue. The first inch of cartilage was resected from the fifth, sixth, and seventh ribs.

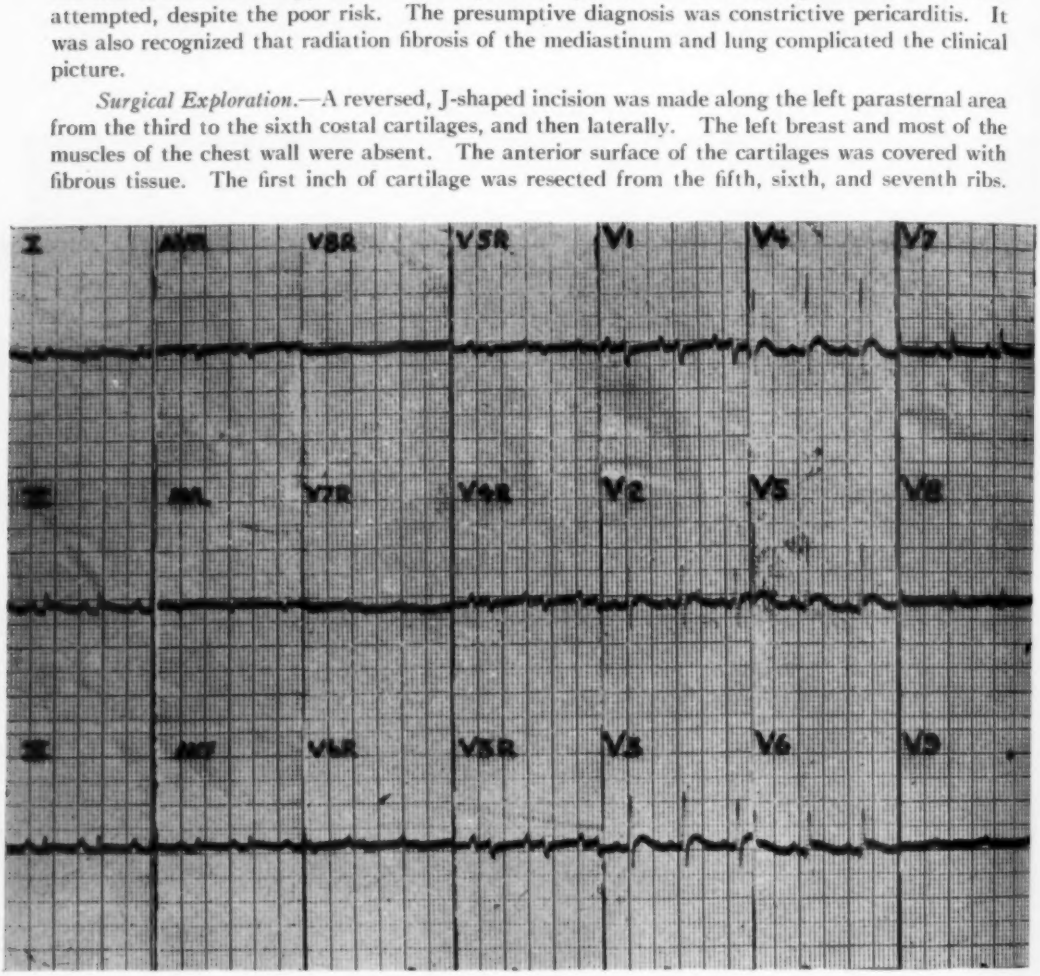

Fig. 5.—Electrocardiogram taken in November, 1950: Compared to the electrocardiogram of September, 1950, the changes indicate an active pericardial process. The voltage is lower. There are now RS-T elevations in the standard leads, aV_F, and in V_2 to V_7. The T waves are still abnormal but are no longer inverted in V_2 to V_6. (Three leads are taken simultaneously by Technicon Cardiograph. V_R is the precordial lead on the right side of the chest.)

The pleura was thickened. The parietal pericardium and the epicardium were firm and adherent. The pericardium was, in turn, adherent to the mediastinal pleura and the chest wall. The inferior pulmonary ligament, the mediastinal pleura, the pericardium, and posterior mediastinum were densely infiltrated with nodular, fibrotic tissue. As the left pleural cavity was entered, a pleural effusion was aspirated. At this point, respirations ceased. Cardiac standstill ensued despite all resuscitative measures.

Essential Gross Anatomic Findings.—

Lungs: There was a fresh hemorrhagic infarct at the base of the right lower lobe. The left upper lobe was shrunken and firm. The cut surface showed extensive replacement of the parenchyma by connective tissue and marked dilatation of the bronchial tree.

Heart: The heart weighed 450 grams. The epicardium was thickened and studded with tumor nodules measuring from 3 mm. to 1 cm. in diameter (Fig. 6). The parietal pericardium was similarly involved. It was diffusely and firmly adherent to the epicardium and completely obliterated the pericardial cavity. On section there was no extension of the epicardial tumor tissue into the myocardium. The plane of cleavage between the parietal and visceral paricardium left a firm, thickened, diffusely constricting epicardium measuring 8 mm. The right and left atria were somewhat dilated and hypertrophied. The endocardium of both atria was thickened. The thickness of the right ventricular wall measured up to 0.5 cm. and that of the left up to 1.6 cm. The valves were normal as were the pulmonary artery and its main branches. There were a few atheromatous plaques in the aortic arch. There was moderate sclerosis of the coronary arteries and some narrowing of the left anterior descending branch. The lumina of the superior and inferior venae cavae were not involved by the pericardial tissue.

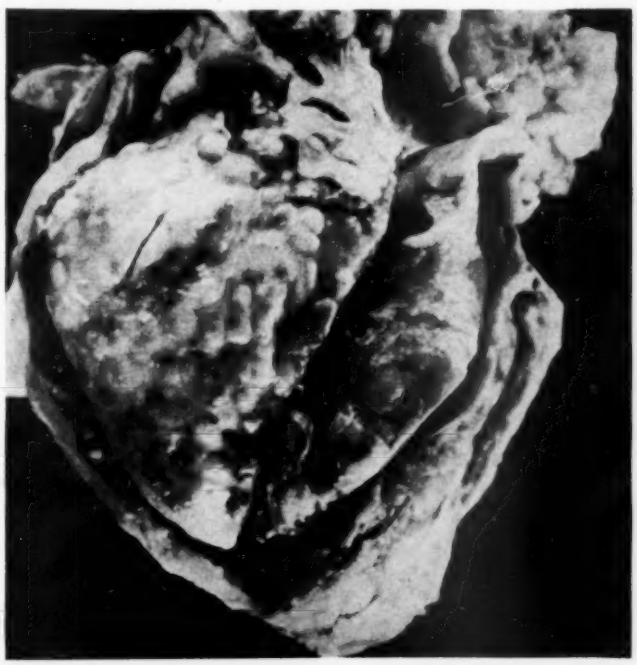

Fig. 6.—Heart: Note the constricting, thickened epicardium and pericardium studded with tumor nodules. The two layers of the pericardium are still adherent at the apex.

Other findings: The abdominal cavity contained at least 500 c.c. of ascitic fluid. The peritoneum was not thickened.

The liver weighed 1,450 grams. The capsule was smooth and thin. The central veins were dilated and were surrounded by extensive depressed yellowish areas. The spleen weighed 150 grams. The capsule was slate gray. The pulp was rubbery and dark purple. Aside from congestion, the remaining organs were essentially normal.

Essential Microscopic Anatomic Findings.—

Heart: The epicardium was markedly thickened and was replaced by tumor tissue consisting of polygonal or low cuboidal epithelial cells arranged in sheets, or in glandlike fashion. The tumor tissue was well demarcated from the underlying myocardium. The supporting stroma was markedly fibrotic and hyalinized (Fig. 7).

Lungs: The parenchyma of the left upper lobe was organized and replaced chiefly by hyalinized connective tissue. The few remaining alveoli and terminal bronchioles were lined by cuboidal epithelial cells. Their lumina frequently contained mononuclear cells which occasionally were

filled with blood pigment. The bronchioles were markedly dilated. The pulmonary arterial tree showed considerable sclerosis and hyalinization of the intima (Fig. 8).

Liver: The lobular architecture of the liver was distorted by markedly distended central veins with pericentral stasis, dilatation of the sinusoids, pressure atrophy, vacuolization, and fatty infiltration of the adjacent liver cells. There were a few focal areas of necrosis. The spleen and kidneys showed marked congestion.

Fig. 7.—Section of the pericardium: Metastatic mammary carcinoma of the pericardium. Note the alveolar arrangement and fibrous stroma. (×500.)

Anatomic Diagnoses.—The anatomic diagnoses included: (1) status fourteen years after left radical mastectomy for duct carcinoma without lymph node metastases; (2) metastatic carcinoma of the pericardium with constrictive pericarditis; (3) radiation fibrosis of the left upper lobe and superior mediastinum; (4) bronchiectasis of the left upper lobe; (5) recent hemorrhagic infarct of the right lower lobe; (6) chronic passive congestion of the liver, spleen, and kidneys; (7) bilateral hydrothorax; (8) chronic adhesive pleuritis of both upper lobes; (9) icterus (hepatic congestion).

DISCUSSION

Clinicopathologic Correlation.—In this patient, the possibility of metastatic carcinoma within the cavity of the right atrium was considered fleetingly. It was disregarded because (1) the primary breast lesion, fourteen years before the present illness, was too remote in time, (2) there were no other metastases, and (3) there was no history of pulmonary embolization. Moreover, the clincal course was not that of metastatic malignancy. According to Mahaim,[2] the possible primary sites for metastasis to the right atrial cavity included carcinoma of the liver, ovary, adrenal gland, thyroid, esophagus, or bronchus and hypernephroma,

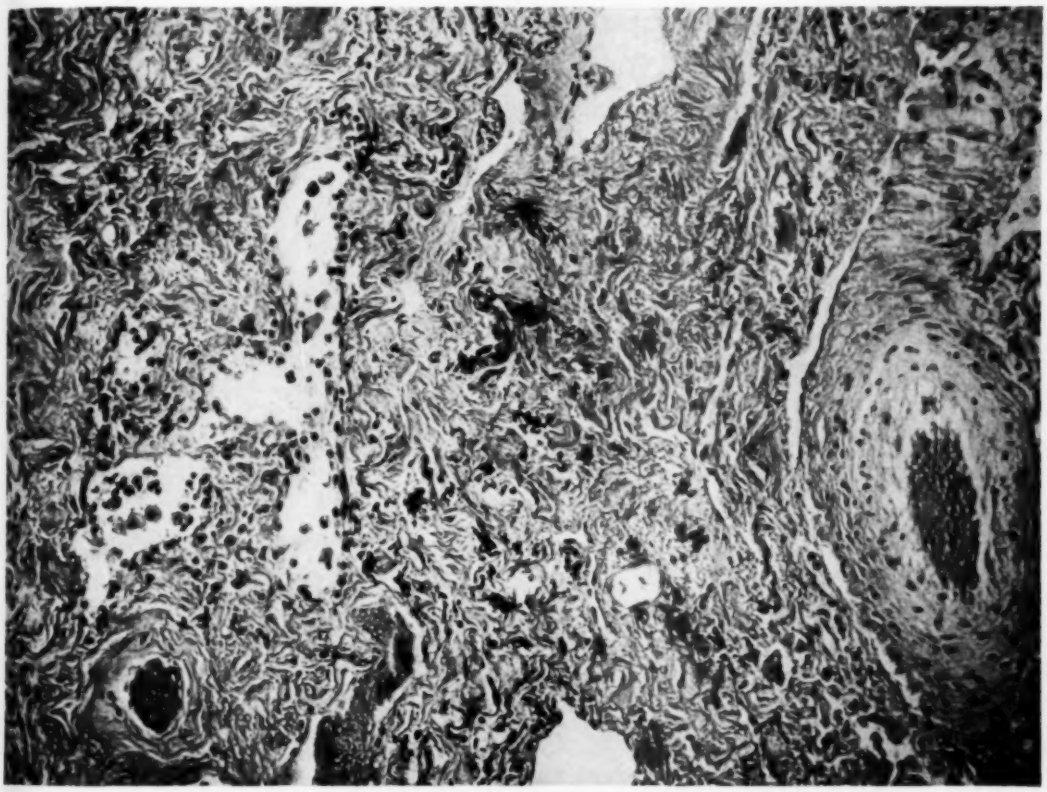

Fig. 8.—Section of lung: Radiation fibrosis of the left upper lobe. The bronchioles (left) are lined with cuboidal cells and contain macrophages. The small artery (right) shows intimal sclerosis. The parenchyma is replaced by dense fibrous tissue. (×325.)

but did not include breast carcinoma. Accordingly, the diagnosis of chronic nonspecific constrictive pericarditis was made in order to explain the severe congestive phenomena in the absence of previous heart disease. Carcinoma as the cause of the pericarditis seemed farfetched. The post-mortem findings clearly indicated that a carcinoma of the breast, successfully resected fourteen years previously, led to solitary metastases to both layers of the pericardium. Moreover, the scirrhus stromal reaction to the neoplastic cells accounted for the dense

constricting pericardial tumor tissue. The tendency to gland formation by the tumor in the pericardium was similar to the original tumor morphology of the primary breast carcinoma (Fig. 7).

Despite the diffuse pericardial and mediastinopleural involvement, there was no tumor tissue in the superior mediastinum. There was no venous obstruction of the superior or inferior venae cavae to account for the congestive signs. The left innominate vein was obstructed by a fibrous band unrelated to tumor metastasis, but directly related to radiation fibrosis. This accounted for the inordinate degree of pitting edema of the left upper extremity.

The Effect of Radiation Therapy.—Roentgen radiation was the primary cause of the fibrosis of the left upper lobe and the adjacent superior mediastinum. Clinically, a tuberculous etiology was discarded because of the absence of tubercle bacilli in the sputum and gastric juice and because there was no past history of tuberculous infection. The possible role of roentgen radiation in adding to the fibrosis and constriction of the pericardium is speculative. The changes in the skin and subcutaneous tissue over the entire left chest and the fibrosis over the ribs are clear-cut radiation effects. Sufficient dosage of x-radiation applied at a short distance from the heart could produce fibrosis and hyalinization of the pericardium, endocardial thickening, and myocardial necrosis. Usually, however, the pericardium and the pleura are resistant to radiation effects.[11,12] Constrictive pericarditis caused by radiation therapy has not been reported. In our case, at least, the possibility exists that radiation contributed to the pericardial fibrosis and was a possible factor in the production of the endocardial fibrosis.

The unusual, broad, paracardiac density (Fig. 4) was also thought to be secondary to radiation. However, surgical exploration and post-mortem examination showed this fibrous plaque to contain tumor tissue.

Unusual Features in the Pathologic Physiology.—In this case, the three unusual clinical features were (1) marked dyspnea, (2) the jaundice, and (3) the electrocardiographic findings. Dyspnea and orthopnea have been considered rare in constrictive pericarditis in contradistinction to the average case of congestive heart failure of comparable severity. Their presence has usually been correlated with the decrease in vital capacity secondary to pleural effusion, ascites, and hepatomegaly.

Our patient's dyspnea and cough were clearly related to the associated radiation fibrosis of the left upper lobe and mediastinum, as well as to the encasement of the left ventricle by tumor tissue. Poor diaphragmatic movement due to fixation by adhesions and tumor, bilateral pleural effusion, hepatomegaly, and ascites contributed to the severe degree of dyspnea. The sudden death early in the operative procedure could be attributed to the marked decrease in vital capacity secondary to the anesthesia and to the opening of the left pleural cavity. In fact, the operative deaths in the series of Andrews and co-workers[10] were also in patients who had pulmonary disease.

To our knowledge, jaundice in chronic constrictive pericarditis has not been reported. In our patient, jaundice was present early in the hospital course when there was no hemoptysis and no sign of pulmonary infarction. The severe con-

gestion, the pericentral atrophy with fat deposition, and the focal necrosis reflected parenchymatous liver damage. Even in the presence of jaundice, all the blood chemical determinations pertaining to liver function were normal except for a fall in the serum albumin.

The usual electrocardiographic changes in constrictive pericarditis include low voltage of the QRS complexes, flattening and inversion of the T waves, and auricular fibrillation or flutter. Changes in the RS-T segment and P waves have not been stressed. In our case, the RS-T elevations and changes in the direction of the T wave indicated an active pericardial injury (Fig. 5). The nature of this injury was difficult to explain in the absence of fever, rapid sedimentation rate, and other evidence of an active tuberculous infection. The presence of actively growing tumor tissue was not suspected. In retrospect, it is suggested that electrocardiographic evidence of acute pericardial injury during the course of constrictive pericarditis should lead to the suspicion of an active pericardial process, either infectious or neoplastic. The changes in the P waves in constrictive pericarditis have been stressed by Soulié and co-workers.[18]

SUMMARY

1. A case of chronic constrictive pericarditis produced by diffuse metastatic carcinoma of the pericardium is presented. The pericardial carcinoma was the *only* metastasis from a primary breast carcinoma completely resected fourteen years previously.

2. The etiology of constrictive pericarditis must include metastatic carcinoma as well ast uberculosis, nonspecific undetermined fibrosis, trauma, and pyogenic inflammation of the pericardium.

3. Radiation contributed to the fibrosis but was not responsible for the constrictive pericarditis. The constrictive encasement of the heart was produced by the scirrhus stromal reaction to the tumor cells.

4. The pulmonary and mediastinal fibrosis secondary to radiation therapy complicated and obscured the diagnosis.

5. Jaundice may occur during the course of constrictive pericarditis and is secondary to chronic congestion of the liver.

6. Electrocardiographic changes of acute pericardial injury (RS-T elevation and T-wave changes) occurring during the course of constrictive pericarditis may indicate either active tuberculosis or the presence of actively growing tumor tissue.

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PERICARDITIS IN PATIENTS WITH LEUKEMIA

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THE two major causes of death in patients with leukemia have been infection and hemorrhage.[1] Since the advent of antibiotics and transfusions, fatal infections have been diminished significantly. Management with antibiotics and transfusions has been shown to prolong the life of children with leukemia,[2] although the survival of patients with chronic myelogenous leukemia remains the same.[2,3] Other complications are now becoming more prominent in leukemic individuals. In the past few years, an increasing number of patients with leukemia have been observed terminally to present findings indicative of cardiac failure. Of forty-three consecutive patients with leukemia observed at the Laboratory of Experimental Oncology, five had pericarditis as an autopsy manifestation. Leukemic pericarditis causing functional impairment[4,5,6] has generally been considered unusual and accorded an insignificant role in the course of this disease.

This report deals with four cases of leukemia in which pericarditis appeared as a serious complication and contributed toward death in three of these patients (Table I). Two of these patients had lymphogenous leukemia, and two had myelogenous leukemia. The fifth patient died at home, and a pericarditis was found at necropsy. The last electrocardiogram taken two weeks before was free of evidence of pericardial involvement.

CASE REPORTS

CASE 1.—M. H., a 58-year-old, white, married housewife, was admitted to the Laboratory of Experimental Oncology on Feb. 1, 1949, with a known diagnosis of chronic myelogenous leukemia of four years' duration. She had been apparently well until approximately four years earlier when she had noted insidious onset of pallor, weakness, bleeding, tender gums, and some vague swellings about the neck. She noted increasing dyspnea on mild exertion. A diagnosis of leukemia was made at that time, and she was treated with parenteral injections of liver, whole blood transfusions, and x-ray therapy to the left upper abdomen. The patient improved, and during the three years before admission she had been quite well and able to do housework, but noticed occasional bleeding gums, night sweats, a tendency to bruise easily, and a fullness in the left upper quadrant. There were no chills or fever.

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TABLE I. PERICARDITIS IN FOUR PATIENTS WITH LEUKEMIA

PATIENT	SEX	AGE	DIAGNOSIS	WHITE BLOOD CELL COUNT	ELECTROCARDIOGRAM	PATHOLOGIC FINDINGS
M. H.	F	58	Myelogenous leukemia (chronic)	24,500 to 131,000	Low and diphasic T waves in V_{4-6}; multifocal ventricular ectopic beats and sinus tachycardia; rate, 120	Organizing fibrinohemorrhagic pericarditis with effusion
B. C.	M	38	Myelogenous leukemia (chronic)	22,000 to 600,000	S-T elevation in III; flat to inverted T waves in II, III, aV_L, aV_F, V_1 to V_6; S-T depression in V_4; rate, 100	Adhesive pericarditis with cardiomegaly; focal involvement of myocardium with myelocytic leukemia
A. L.	M	30	Lymphatic leukemia (acute)	215,000 to 536,000	Low to diphasic T waves and low voltage QRS throughout standard and extremity leads and sinus tachycardia; rate, 140	Early fibrinous pericarditis with effusion and massive infiltration of pericardium with primitive lymphoid cells
M. D.	F	7	Lymphatic leukemia (acute)	775 to 2,500	Not technically satisfactory	Acute fibrinous pericarditis with infiltration of pericardium with lymphoid cells

Physical examination revealed a pallid, obese, lethargic woman in no acute distress. Eyes, ears, nose, and throat were within normal limits. The heart revealed no enlargement or murmurs. Blood pressure was 110/70 mm. Hg. The lungs were clear to percussion and auscultation. The abdomen showed a generous panniculus and a ventral hernia. The spleen was firm, smooth, nontender, and enlarged to the midline and down to the left iliac crest. The liver was palpable 7 cm. below the right costal margin with a sharp, nontender edge. The pelvic and rectal examinations were negative.

The entry hemogram revealed a white blood cell count of 61,000 with a differential count of polymorphonuclear neutrophils 17, bands 11, metamyelocytes 19, polymorphonuclear basophils 11, polymorphonuclear eosinophils 4, myelocytes 24, and lymphocytes 14.

Progress and Treatment.—The patient received Methopterin,* 2 to 5 mg. daily intramuscularly, from Feb. 10, 1949, through March 13, 1949, without favorable effect. Aureomycin, 3 Gm., was given daily from March 31, 1949, through April 5, 1949. The patient received six whole blood transfusions.

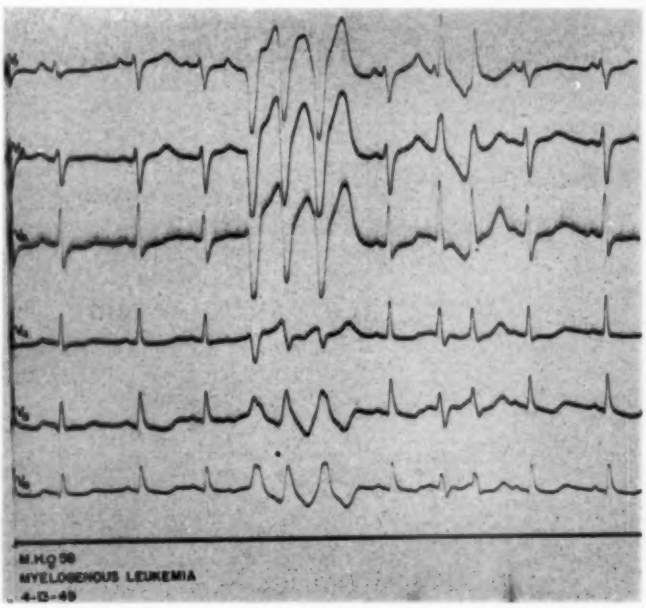

Fig. 1.—A simultaneous, precordial, six-lead electrocardiogram taken twenty-four hours prior to death.

Nevertheless, the course was downhill with marked weight loss, weakness, increasing dyspnœa, decreased pulse pressure, and tachycardia. Electrocardiograms were taken on March 16, 1949, and April 13, 1949, because of the clinical suspicion of pericarditis with effusion (Figs. 1 and 2). On April 14, 1949, the patient suddenly developed marked cyanosis and inaudible heart sounds and died within a few minutes.

Post-Mortem Findings.—Massive dilatation of the pericardial sac, which contained at least 1 L. of serosanguineous fluid, was found. The pericardium was thickened by dense hemorrhagic and fibrinous deposits, with dilatation of the major veins. The heart weighed 500 grams, and the epicardium was obscured by masses of fibrin. The left ventricle was 1.5 cm. in thickness and showed dilatation. The myocardium appeared intact, and the endocardium was smooth. The right ventricle showed no abnormality except for slight hypertrophy (0.4 cm.). Microscopically, the epicardium was thickened by masses of infiltrating myeloid cells of all degrees of

*Kindly supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

differentiation. The outer layers were covered by fibrin and organizing fibroblasts, with minimal bleeding and deposition of blood pigment. Careful survey of the heart showed only slight subendocardial and perivascular infiltration. The remaining findings were those of a typical myelogenous leukemia with hepatosplenomegaly and generalized lymphadenopathy. The bone marrow was massively replaced. There was also a left hydrothorax of 1 L., slight abdominal ascites, and peripheral pitting edema. In addition, a chronic colitis and terminal ileitis were found (Flexner bacillus).

CASE 2.—B. C., a 38-year-old, clerical worker, first entered the Laboratory of Experimental Oncology on March 17, 1950, with complaints of dyspnea, anorexia, and weakness of two months' duration.

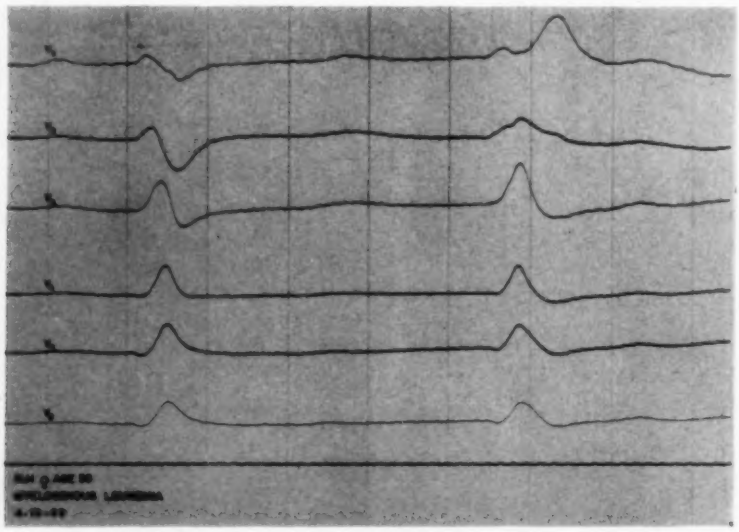

Fig. 2.—Two complexes at rapid paper speed. Note the different right precordial leads without alteration of V_{4-6}.

The important findings on physical examination included a temperature of 38° C., pallor, dyspnea at rest, and moderate exophthalmos. The trachea was in the midline, and the lung fields were clear. The anterior and posterior cervical chains showed numerous shotty, small, nontender nodes. The heart was not enlarged to percussion, and there were no murmurs, friction rubs, or thrills. The rhythm was regular and the rate 100. Blood pressure was 135/90 mm. Hg. The liver edge was felt 3 fingerbreadths below the right costal margin, smooth and nontender. The spleen was firm, nontender, and enlarged to the level of the umbilicus. Aside from moderate pitting edema of both legs and the sacral area, the remainder of the general physical examination was normal.

The entry hemogram revealed a white blood cell count of 128,000 with a differential count of polymorphonuclear neutrophils 45, bands 8, metamyelocytes 9, polymorphonuclear basophils 2, polymorphonuclear eosinophils 2, myelocytes 14, normoblasts 4, and lymphocytes 20. The serum hormonal iodine was 5.2 μg per cent.

Two weeks after entry the patient developed increasing dyspnea at rest and marked ankle edema. The physical examination revealed no venous distention, but the area of cardiac dullness was increased both to the left and right. The heart sounds were muffled. The lung fields were clear except for a few moist râles at the left base posteriorly. Expansion of the left chest was decreased. A chest film on March 28, 1950, revealed marked enlargement of the cardiac shadow in all diameters (Fig. 3). A coarse pericardial friction rub was audible over the third intercostal space near the left sternal border.

A diagnosis was made of pericarditis with effusion, probably on a leukemic basis, resulting in congestive failure. An electrocardiogram taken during this period showed S-T segment deviations and T-wave changes consistent with the evolution of an acute pericarditis (Fig. 4).

The patient was placed on a 500 mg. sodium diet and given ammonium chloride with mercurial diuretics; a prompt diuresis occurred, followed by clearing of the lung fields and peripheral edema. Digitalis was not employed. The friction rub became louder and audible over the entire precordium but disappeared within three days. The patient improved gradually and was discharged on April 28, 1950, after receiving several transfusions.

The patient subsequently re-entered the Laboratory for radiophosphorus therapy and eventually died on March 23, 1951.

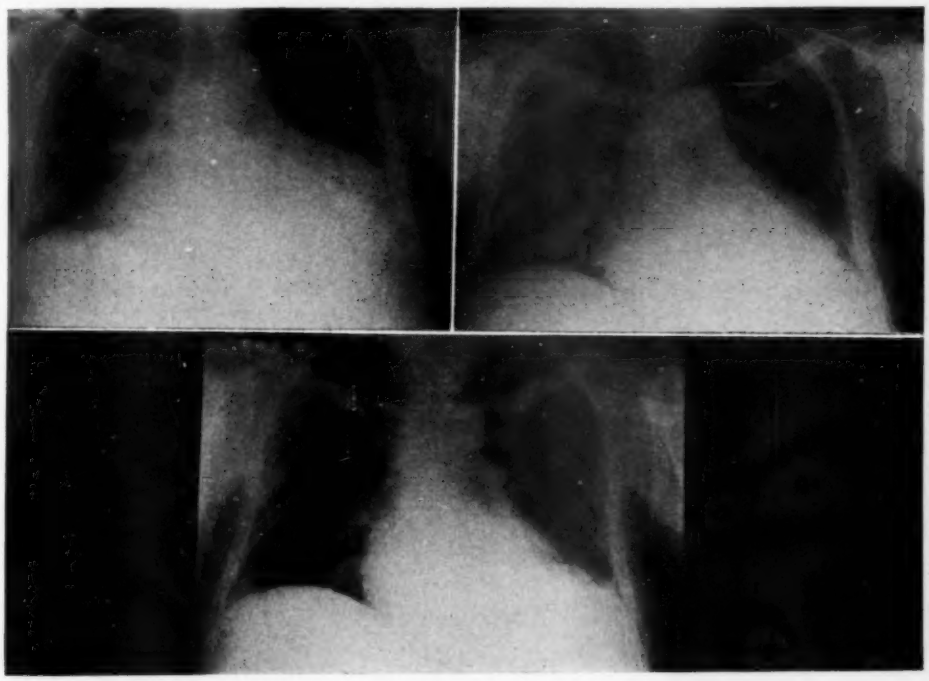

Fig. 3.—Chest films of patient B. C. before, during, and after pericardial effusion.

Post-Mortem Findings.—The pericardial sac was enlarged and had a white, opaque color The epicardial space was completely obliterated by fibrous adhesions that could be separated only with considerable difficulty. The major veins were markedly distended. The heart weighed 510 grams and was increased in size due to a thickened epicardium and prominent dilatation of the right ventricle. The myocardium appeared intact except at the base of the right ventricle where a 1 cm. area of thinning and pallor was noted. The valves grossly were delicate.

On microscopic examination, the pericardium and epicardium showed masses of organizing fibrous tissue diffusely infiltrated with myeloid cells of varying degrees of differentiation. Some areas showed old hyaline scar tissue, while others had freshly deposited fibrin. A section through the area of pallor in the right ventricle showed a dense accumulation of myeloid cells which were infiltrating the myocardium and endocardium, with hydropic changes of the myocardium. Also, the tricuspid valve showed a focal accumulation of myeloid cells associated with fibrin and organizing fibroblasts. The remaining findings were those of a generalized lymphadenopathy, hepatosplenomegaly, and massive replacement of the bone marrow. A severe generalized bleeding tendency was evident with bilateral hemorrhages into the adrenals.

CASE 3.—A. L., a 30-year-old Negro man, was admitted to the Laboratory of Experimental Oncology with a four-month history of illness. The symptoms at the onset were those of nasal congestion and sinusitis, treated for four weeks without success, at which time the patient noted marked generalized lymphadenopathy. He also noted increased weakness and marked weight loss. A high leukocyte count with typical hematologic characteristics of lymphatic leukemia was found by his physician.

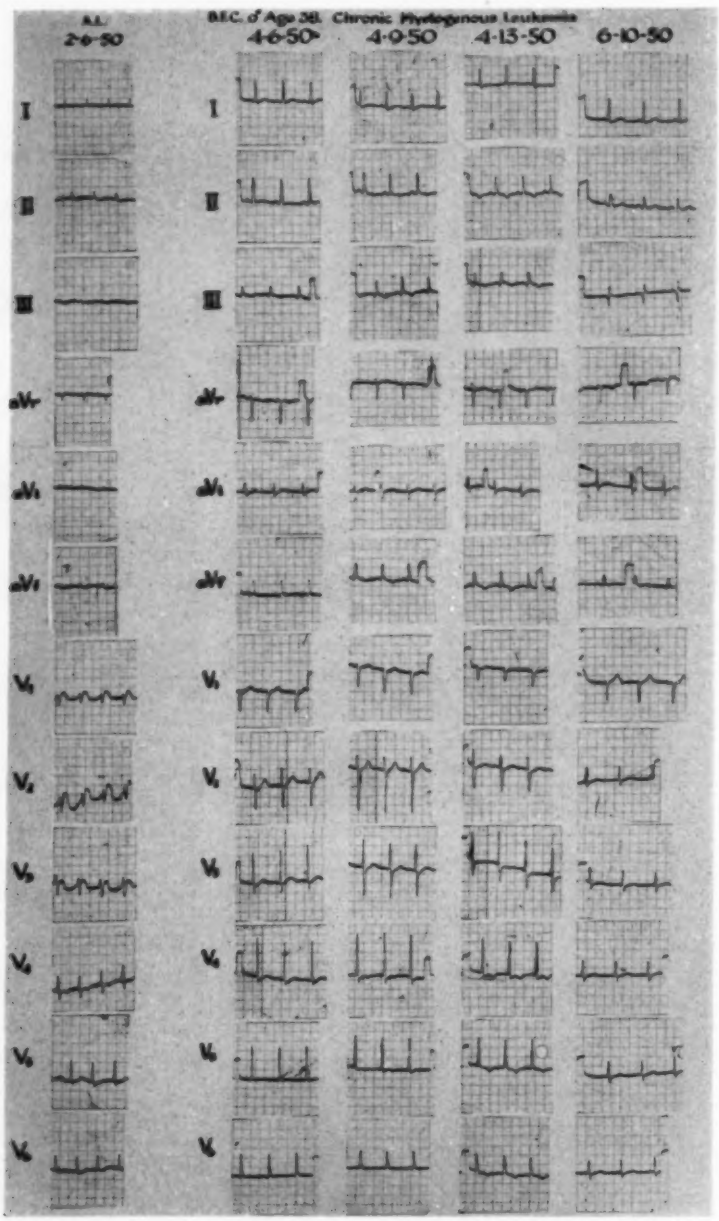

Fig. 4.—Electrocardiograms of patients A. L. and B. C.

The pertinent physical findings at the time of entry to the Laboratory on Dec. 23, 1949, were marked, generalized lymphadenopathy, hepatosplenomegaly, left pleural effusion, and a typical blood and bone marrow picture of lymphatic leukemia.

Treatment and Course.—The patient's course was marked by a very high white count, varying between 200,000 and 500,000 per cubic millimeter, 99 per cent of which were lymphocytes. Left pleural fluid continued to form at a very rapid rate.

ACTH plus supportive treatment was administered, and the patient required frequent thoracenteses; 12 L. of clear yellow fluid were removed over a ten-day period. Two days prior to death, the patient's pulse rate increased, and it was felt that he had developed a pericarditis with effusion. Repeated electrocardiograms taken before and after removal of fluid showed a rapid rate and ST changes consistent with a pericarditis (Fig. 4). On Feb. 7, 1950, the day of his death, it was noted that the pleural fluid was under positive pressure. However, removal of more than 1,700 c.c. caused respiratory distress, and aspiration was discontinued. That evening the patient died quietly in his sleep.

Post-Mortem Findings.—The examination showed approximately 2 L. of fluid in the left pleural cavity, 1 L. in the right pleural cavity, and abdominal ascites of 1 L. The pericardial sac contained 500 c.c. of a serosanguineous fluid without adhesions. The heart weighed 305 grams and showed slight opacity of the epicardium with a slightly irregular surface. Microscopically, the myocardium and endocardium were normal. The epicardial fat showed focal massive infiltration with sheets of small lymphoid cells. There was associated bleeding with fibrous thickening of the tissue. The remaining findings were those of acute lymphatic leukemia with generalized lymphadenopathy, hepatosplenomegaly, and bone marrow infiltration.

CASE 4.—M. D., a 7-year-old, white girl, had shown symptoms of increasing pallor, weakness, generalized bone pain, and nonproductive cough since April, 1949. Fever, hepatosplenomegaly, and progressive anemia were found. A diagnosis of subleukemic lymphatic leukemia was made, and during the entire period of observation at the Laboratory of Experimental Oncology from May, 1949, the peripheral blood leukocyte count never exceeded 2,900. She re-entered the Laboratory on Nov. 10, 1949, after four days of malaise, abdominal pain, and watery diarrhea with a temperature of 41° C. Examination showed her to be acutely ill with hepatosplenomegaly and generalized abdominal cramplike pain and tenderness. Following aureomycin therapy the temperature fell, and she showed clinical improvement, although at this time the leukocyte count was 775. She continued to improve and was discharged to her home.

She re-entered on Dec. 13, 1949 because of four days of abdominal pain and distention with a liquid, foul-smelling diarrhea. The temperature was 39.6° C. The lung fields were clear, and the heart was not enlarged to percussion. The abdomen was distended and tender in all quadrants; peristalsis was absent, and the spleen was markedly enlarged, occupying the entire left abdomen. No change was noted in the lymph nodes which had always been minimal in size. The white blood count was 2,400 with 97 per cent lymphocytes. The patient was given transfusions and penicillin. A tachycardia of 160 was noted, and the anterior cardiac dullness was found to be enlarged to the left anterior axillary line. The heart sounds were of fair intensity. Pericarditis was suspected, but electrocardiograms were not technically satisfactory. The pulse became irregular, and respirations suddenly ceased within a few hours.

Post-Mortem Findings.—The pericardial sac was distended by serosanguineous fluid that was rich in fibrin and showed signs of recent precipitation on the underlying pericardial membrane which itself was smooth and glistening. The heart weighed 130 grams and showed no other gross abnormalities. Microscopic study of sections through the region of the left ventricle showed masses of primitive lymphoid cells within the pericardial and epicardial tissues. There was slight subendocardial infiltration. The myocardial cells themselves were of normal size and were well preserved. A diagnosis of acute fibrinous effusion was evident. The remaining findings confirmed the diagnosis of acute lymphatic leukemia. In addition, there was an incomplete perforation of the colon with partial walling-off by dense adhesions.

DISCUSSION

Leukemic infiltrations of the heart and its investing membranes are believed to occur frequently, but this topic has received little attention in the medical literature. As early as 1871, Virchow[7] stated that he had seen small lymphoid tumors under the pericardium in well-proved cases of leukemia. Forkner[1] stated that in leukosarcoma, involvement of the pericardium and of the heart often occurs. Cardiac involvement was demonstrated to be frequent in leukemia by Kirshbaum and Preuss.[8] These authors found at post-mortem examination that the heart was involved in 34 per cent of 123 fatal cases of leukemia and that infiltration of this organ was second in frequency only to that of the kidney, which was involved in 63 per cent of the total cases. This same study also revealed that the highest percentage of cardiac involvement occurred in acute stem-cell and lymphatic leukemia. Hemorrhages in the epicardium were seen most often by these workers in acute stem-cell and acute myelogenous leukemia.

The incidence of pericardial infiltration with leukemic cells in patients with leukemia is high and must be considered as part of the illness. Disturbance of cardiac function due to such infiltration is generally conceded to be a rare occurrence[5,6]; but the detection of such abnormalities is most difficult, since it often occurs during the terminal phase of the leukemic state and would be obscured by other symptomatology. An awareness that pericardial involvement may occur in practically every case of leukemia at some time has enabled an earlier detection of this phase of the illness and accordingly an observation of the associated clinical phenomena. Most studies of leukemic pericardial involvement have been from post-mortem material so that the period at which the cellular infiltration is initiated has not been ascertained. It is most probable from clinical observation, however, that the infiltration is present for a long time with an acceleration of the process as the disease advances and during exacerbation.

In three of the four cases reported herein, the leukocyte counts were above 100,000, and the count was increasing rapidly. Jaffe[9] studied ten patients with leukemia for their defense reactions during inflammation. Two showed a fibrinous pericarditis at necropsy. Both patients had myelogenous leukemia, one with a leukocyte count of 31,000 to 192,000, the other with 90,000 per cubic millimeter. Friedman and Silverman[10] recently reported a similar case of pericardial effusion in a patient with chronic myelogenous leukemia who recovered and suggested its similarity to that of the acute serofibrinous pericarditis following a respiratory infection described by Levy and Patterson.[11] More infiltration of tissues would be expected when the leukocyte count is high than when it is low. On the other hand, one patient (M. D.) had an acute fibrinous effusion with a white cell count which never exceeded 2,500 cells per cubic millimeter. The amount of cellular infiltration was little in the myocardium and marked in the pericardial fat.

Another cause of pericarditis under these circumstances could be hemorrhagic foci into the epicardium with effusion from the attendant irritation of the serous surfaces. Hemorrhagic areas beneath all serous membranes are found commonly at post-mortem examination in leukemic individuals. However, the

petechial areas are not necessarily those involved with the cellular infiltration which often is more diffuse. The febrile pattern which almost always is present at this time could have its origin in any of the above pathoses.

Wintrobe[12,13] has pointed out that the symptoms and signs of heart failure may develop in leukemia, chiefly as the result of cardiac dilatation due to anemia and anoxemia. Dyspnea, tachycardia, cyanosis, and signs of increased venous pressure could also result in part from myocardial infiltration by leukemic cells. In the past these symptoms have been ascribed to the protean nature of the leukemic process itself, due most likely to fever and anemia. The septum of the atrioventricular conduction system, because of its loose vascular structure, may be particularly predisposed to infiltration with subsequent rhythmic disturbances or heart block.[14] In febrile or anemic patients, heart block can be easily overlooked, and, for this reason, routine electrocardiography on leukemic patients is suggested.[1,4] Blotner and Sosman[6] have reported the successful treatment of heart block in a leukemic patient, believed due to leukemic infiltration, with x-ray therapy over the heart. Hydropericardium or hemopericardium from pericardial implants may be responsible for the sudden development of cardiac failure. Pericardial paracentesis may be essential in these cases. The sudden appearance of cardiac symptoms in the absence of previous cardiac disease in a leukemic patient should make the clinician suspicious of infiltration of the heart or pericardium. If this complication is recognized early, symptomatic relief can be afforded, for a time at least, by routine cardiac therapy of rest, salt restriction, oxygen, and digitalization.

SUMMARY

1. Four leukemic patients who developed pericarditis during the course of their illness are reported. Adhesive pericarditis was found at post-mortem examination in two patients with myelogenous leukemia. In the remaining two patients with lymphogenous leukemia, effusion was the major finding. One of the patients with chronic myelogenous leukemia recovered from an episode of pericarditis and survived for eleven months.

2. The electrocardiographic changes in three patients were characterized by tachycardia, low voltage, elevation of ST complexes, and flat to inverted T waves.

3. Peripheral blood leukocyte counts above 100,000 were present in three of the four patients. In the remaining patient, the peripheral blood leukocyte count was consistently below 2,500 per cubic millimeter.

4. It is suggested that pericarditis with cellular infiltration occurs more frequently than usually suspected in leukemic patients and may often contribute to their death.

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LEFT ATRIAL ENLARGEMENT

The Optimum Roentgen Method for Its Demonstration

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THE importance of left atrial enlargement in the diagnosis of rheumatic mitral valvular disease has long been appreciated. Some have even considered its recognition secondary only to the pathognomonic apical diastolic murmur as a diagnostic criterion.

The conventional upright posteroanterior, lateral, and both anterior oblique chest films afford a great deal of important diagnostic information about the heart. The posteroanterior and the anterior oblique views with the esophagus opacified by thick barium add further valuable data and form the present accepted routine for cardiac studies. A right anterior oblique view with the esophagus opacified has become commonly accepted as the best single technique for demonstration of left atrial enlargement.[1,2]

Except for brief mention of the right lateral view,[3,4,5] the literature is silent concerning lateral studies in general. A critical comparative study has convinced us that the left lateral teleroentgenogram with barium in the esophagus is superior to the other views.*

In our experience enlargement of the left atrium is generally better demonstrated in the left lateral view than in the right anterior oblique view. In addition, it is more accurate in the recognition of minimal left atrial enlargement and is of value in distinguishing left atrial from left ventricular enlargement. This is due to the fact that the primary enlargement of the left atrium is posterior upon the esophagus and that such displacement backward is, on spatial considerations alone, best visualized in the lateral view. The left lateral view is preferred to the right only because the structures being studied are located slightly to the left of the midline.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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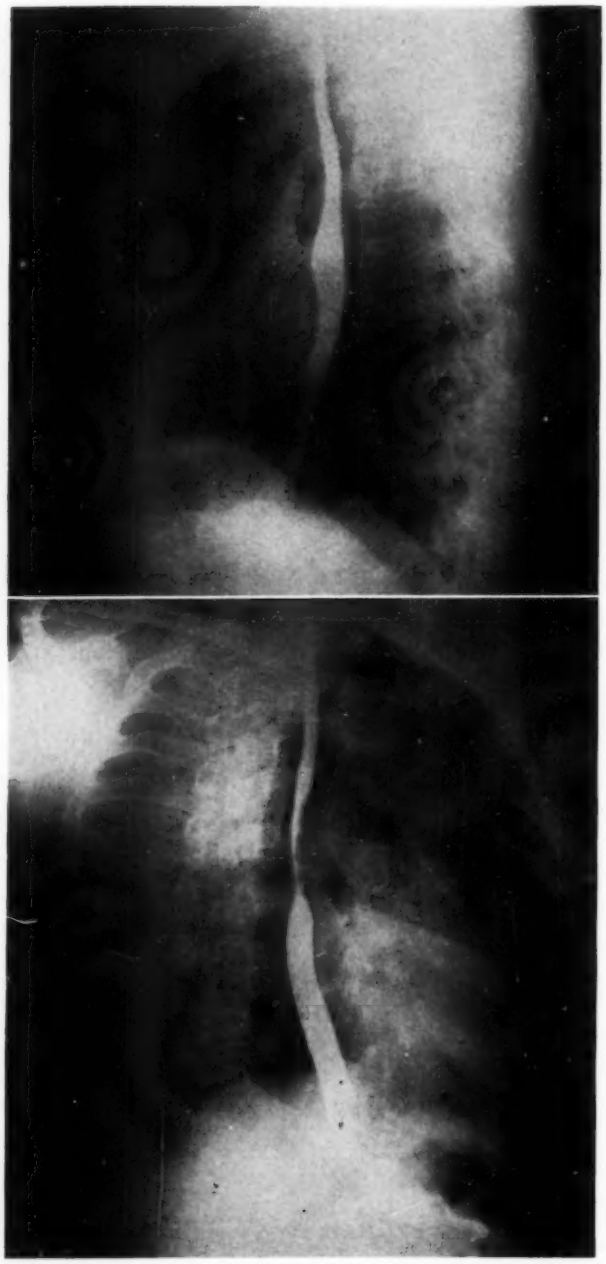
*The origin of the use of the routine left lateral view is not definitely known to us. However, we are indebted to Dr. Hugh M. Wilson, Professor of Radiology at Washington University School of Medicine who taught one of us (H. G. J.) the use of this method. Another one of us (M. H. P.) was aware of the feasibility of the use of this method approximately fifteen years ago while working with Dr. I. Seth Hirsch.

A.



B.

Fig. 1.—The left lateral view (*A*) shows a typical indentation of the barium-filled esophagus by an enlarged left atrium, while the right oblique view (*B*) is essentially negative.

TABLE I. DEGREE OF LEFT ATRIAL ENLARGEMENT IN FORTY-NINE PATIENTS WITH RHEUMATIC MITRAL DISEASE AND ONE WITH "MITRALIZED" ARTERIOSCLEROTIC HEART DISEASE IS RATED FROM ONE TO FOUR "PLUS" IN TWO VIEWS, CONTRASTED IN ADJACENT COLUMNS

NO.	INITIALS	RIGHT ANTERIOR OBLIQUE VIEW	LEFT LATERAL VIEW	X-RAY NO.
1	J. K.	0	+	90321
2	W. O'H.	0	++	88649
3	B. J.	0	++	90111
4	S. McN.	0	++	45116
5	W. B.	0	++	95459
6	L. S.	0	++	84036
7	J. F.	+*	+++	87547
8	P. L.	+*	++	93224
9	J. M.	+	+++	16563
10	P. D.	++	+++	88126-A
11	P. L.	+	+++	82882
12	J. McK.	+	++	26414
13	J. G.	+	+++	58573
14	O. G.	+	++	31261
15	N. A.	++	+++	89904
16	G. T.	++	+++	89504
17	F. G.	++	+++	86811
18	G. O.	+	++	69619
19	S. F.	++	++++	63125
20	J. M.	++	+++	79634
21	J. McK.	++	+++	92110
22	G. L.	++	+++	76085
23	D. D.	+++	++++	85966
24	A. H.	++	+++	79686
25	J. W.	+	++	86921
26	T. H.	+++	++++	86243
27	J. K.	+	++	57612
28	H. B.	+	++	52066
29	T. McK.	+	++	63283
30	V. M.	+	++	88973
31	F. K.	+	++	41828
32	A. O.	+	++	85650
33	J. Q.	++	+++	88335
34	M. O.	+	++	94927
35	S. T.	+	+++	93999
36	A. B.	+++	++++	63305
37	S. S.	+	++	84724
38	B. P.	++	+++	95818
39	W. O'N.	+	+++	94363
40	P. N.	++++	++++	87245
41	B. K.	++	++	89905
42	T. P.	++	++	77560
43	D. G.	+++	+++	29005
44	R. McI.	++	++	4340
45	G. M.	+	+	48070
46	J. V.	++	++	50447
47	F. M.	+	+	93763
48	J. L.	++	+	81317
49	G. S.	++	+	54067
50	J. K.	+++	++	94148

*These two cases presented such minimal findings in the right anterior oblique view that they were considered equivocal.

ANATOMY

The esophagus courses caudad through the thorax as a fairly straight tube which conforms somewhat to the anterior curvature of the thoracic spine. It lies anterior to the vertebral bodies throughout its extent, maintaining a distance

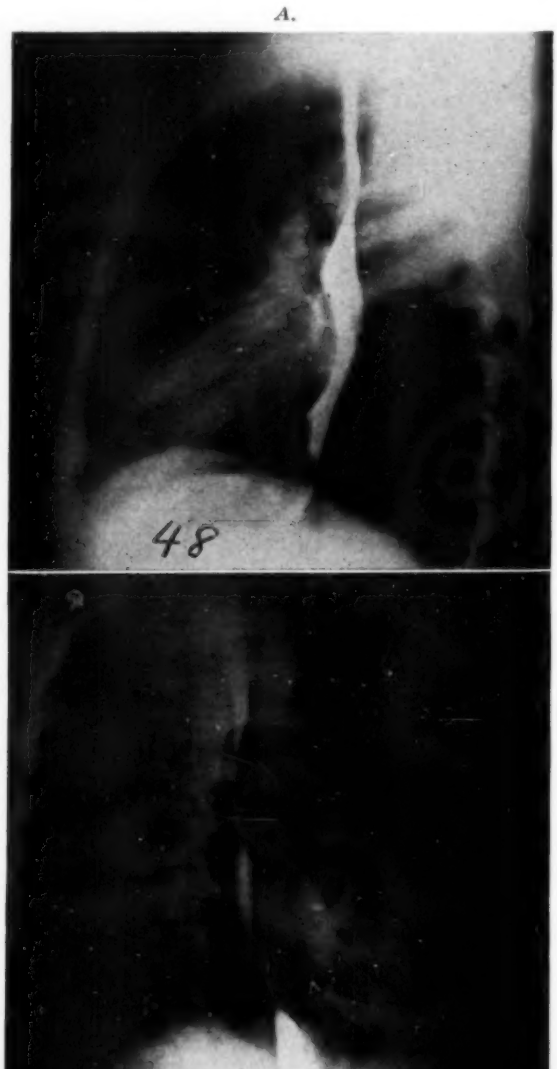


Fig. 2.—The left lateral view (*A*) shows deep indentation and moderate backward displacement of the esophagus by the enlarged left atrium; the right oblique view (*B*) shows this enlargement only minimally. The left ventricle is not enlarged (*C*).

of 1 to 3 cm. between its posterior wall and the spine. In its upper one-third the anterior and left walls of the esophagus are indented by the arch of the aorta. Just below this, the esophagus is indented by the left main bronchus. Its middle one-third lies in close contact anteriorly with the dorsal surface of the left atrium, which essentially is a posterior component of the heart. The remaining lowermost one-third is in contact anteriorly with a small portion of the left ventricle. In its lower two-thirds the esophagus is anterior and to the right of the descending aorta. With enlargement of the left atrium the esophagus is first indented on its anterior wall and then displaced posteriorly and ultimately to the right. In rare cases it may be displaced toward the left.[6] Lateral displacement may be partially due to slight degrees of scoliosis. This indentation and displacement is most evident in the middle one-third of the esophagus where posterior impingement on the barium-filled esophagus is well seen. In the left lateral view, narrowing of the esophageal lumen is clearly visualized, and posterior displacement diminishes or obliterates the space between esophagus and spine (see Figs. 1 to 8).

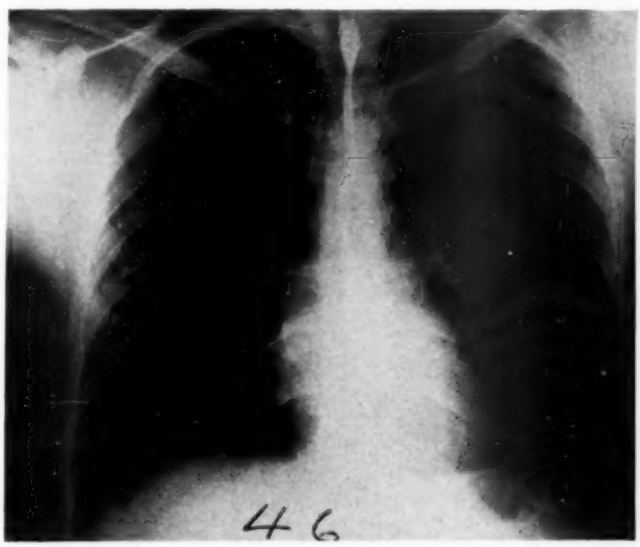


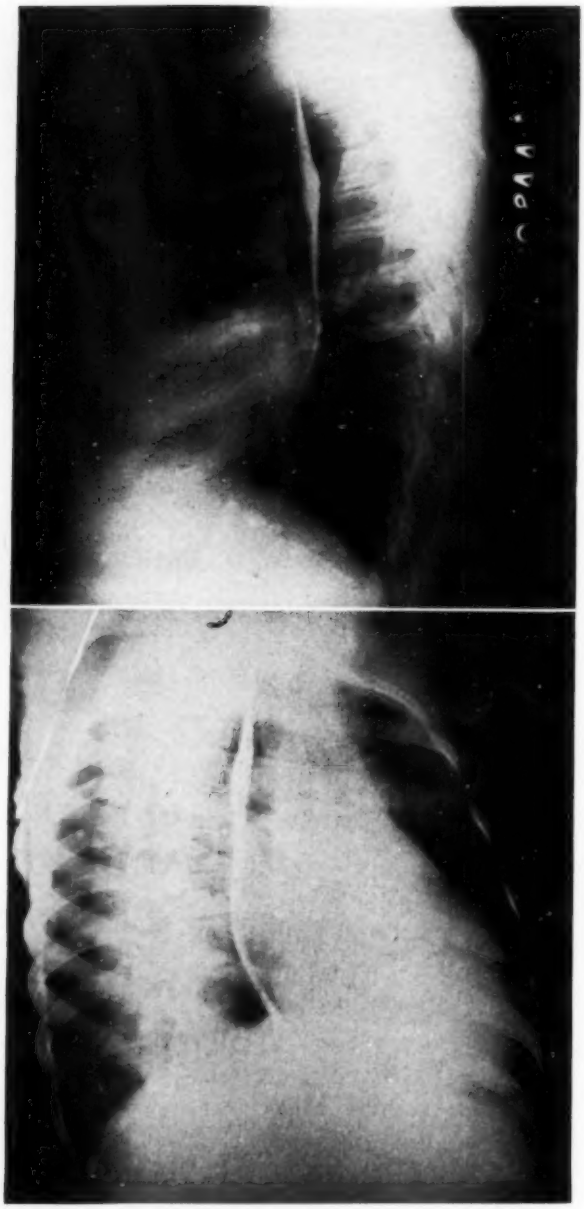
Fig. 2, *C*. *(For legend see opposite page.)*

TECHNIQUE

At a suitable interval following deglutition of a mouthful of barium paste, a left lateral teleroentgenogram in deep inspiration is taken. This, in conjunction with posteroanterior and oblique chest films with the esophagus opacified, provides a basis for comparison of the lateral with the right anterior oblique view.

This technique has been in use routinely at this hospital since 1947 in patients with rheumatic or other heart disese with known or suspected left atrial enlargement. Suitable cases so studied form the material of this report.

A.



B.

Fig. 3.—The left lateral view (*A*) shows thinning of the barium stream and backward displacement in greater degree than does the right oblique view (*B*). Note that in the presence of an enlarged left ventricle (*C*) the heart is apparently in contact with the esophagus all the way to the diaphragm in contrast to the clear space between the heart and the lowermost portion of the esophagus seen in Figs. 1 and 2.

MATERIAL

Fifty men ranging in age from 20 to 65 years were selected at random from our records over the past three years. All but one were clinically diagnosed as having rheumatic heart disease with mitral valve involvement. The one exception had arteriosclerotic heart disease with "mitralization" and a roentgenographically enlarged left atrium indistinguishable from that of a rheumatic patient. About one-half of the patients also had aortic valve lesions, but this was of interest only in regard to the differentiation of left atrium from left ventricle. All had teleroentgenograms with barium in the esophagus in addition to other conventional studies. The technique was uniform. Left atrial enlargement was demonstrated in at least one view, and other evidences of left atrial enlargement (e.g., elevation of the left main bronchus and double contour to the right of the spine) were noted when present. Patients not showing left

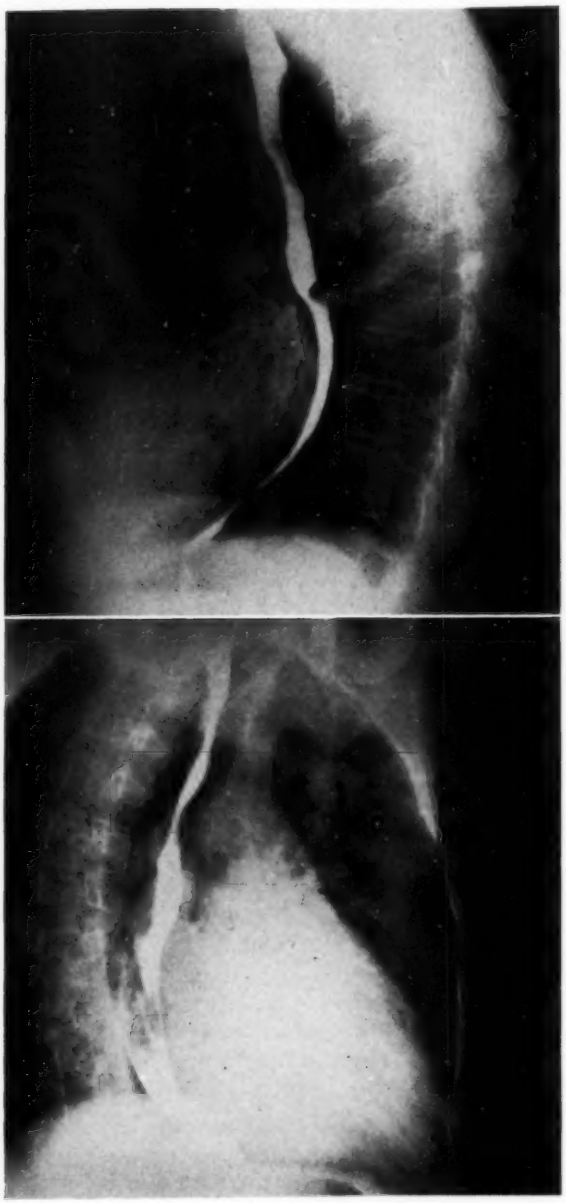
Fig. 3. *C.* *(For legend see opposite page.)*

atrial enlargement, those in whose cases the technique was defective, and those with marked distortion of the esophagus from other causes were excluded. The degree to which both the right oblique and left lateral views demonstrated enlargement of the left atrium was rated from one to four "plus," and the results were tabulated (Table I). Any error involved in comparing studies of different dates on any given patient was avoided by using only films taken at the same time or within a few days of each other.

RESULTS

It will be seen from the table that of fifty cases the left lateral view was superior to the right oblique in thirty-nine. In six of these the enlargement could not be seen in the right oblique view at all, while it was definite in the left lateral. On the other hand, there was no instance in which the oblique view

A.



B.

Fig. 4.—This patient shows an immense left atrium, indenting and distorting the esophagus markedly in the left lateral view (*A*), while the right oblique view (*B*) displays it to less advantage. The lateral view also differentiates very well the relations of the enlarged left atrium and the enlarged left ventricle (*C*) with the esophagus. There is, indeed, a small triangular clear space between the convexities of these two enlarged chambers as they impinge upon the esophagus in the radiograph with the atrium above and the ventricle below.

demonstrated left atrial enlargement and the left lateral view did not demonstrate it. In two other cases the findings in the right oblique view were so equivocal that it could not be decided finally whether or not left atrial enlargement was present. In these cases the left lateral view was diagnostic.

In only eight cases was the degree of enlargement equal in both views, and in only three was the right oblique superior to the left lateral view in demonstrating left atrial enlargement.

Fig. 4, *C*. *(For legend see opposite page.)*

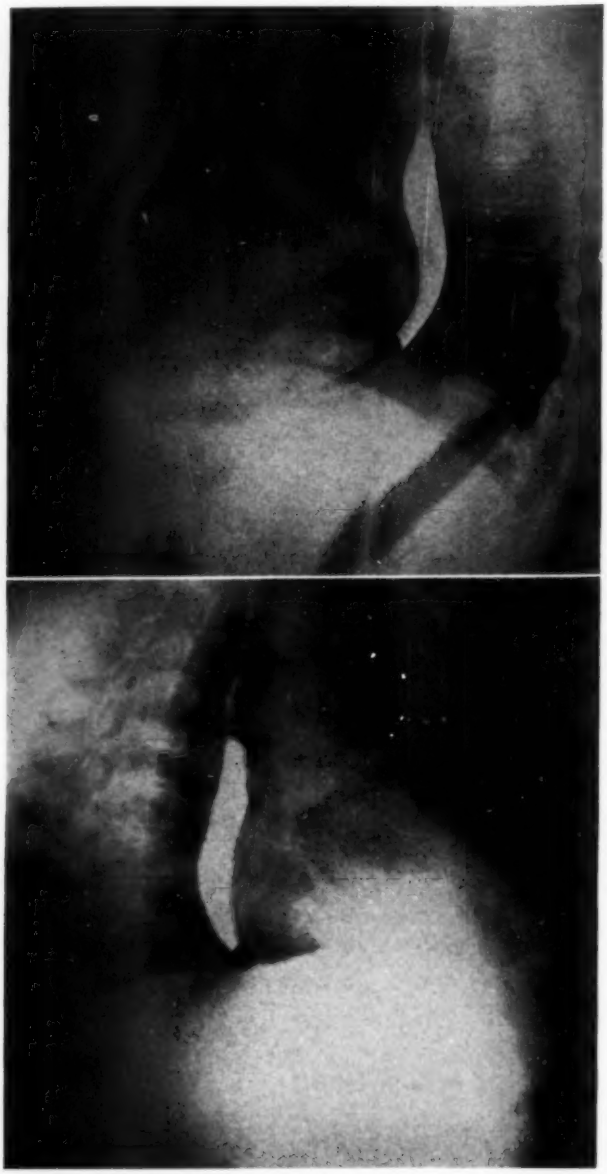
DISCUSSION

The left lateral upright chest film in conjunction with the barium-filled esophagus was found superior to the right anterior oblique position in 78 per cent of fifty cases, equal to it in 16 per cent, and inferior in only 6 per cent. It has shown left atrial enlargement when the right oblique view failed to do so (six cases) and has never been negative when the right oblique was positive for left atrial enlargement. The value of the left lateral position for diagnosis of early, minimal left atrial enlargement is thus evident.

An additional factor to be considered is that in the left lateral projection there is far less confusion from shadows caused by superimposed cardiac, diaphragmatic, and pulmonary structures than there is in the right oblique position. This aids distinctly in the precise definition of the involved atrium and its distinction from other cardiac chambers (e.g., left ventricle), which may or may not also be abnormal. The indentation and/or displacement of the barium-filled mid-esophagus posteriorly by an enlarged left atrium is easily differentiated in

the left lateral view from the still lower segment of the esophagus which is frequently indented, slightly displaced, or overlapped by posterior enlargement of the left ventricle.

A.

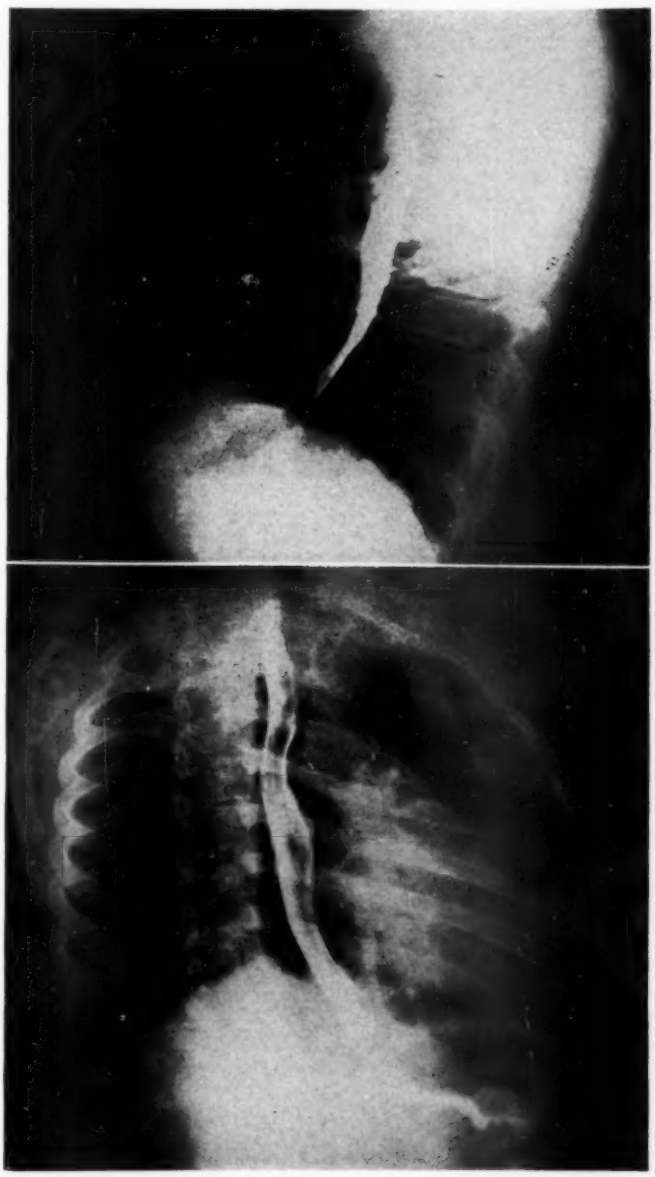


B.

Fig. 5.—Left atrial enlargement posteriorly is seen far better in the left lateral (*A*) than in the right oblique view (*B*). In this case the left ventricle was also prominent; the lowest segment of esophagus shows its posterior enlargement.

The technical simplicity of positioning the patient for a left lateral projection is worthy of emphasis. Satisfactory right oblique studies require preliminary fluoroscopy to determine the optimum angle for best results.[7] This a technician cannot do, and it imposes an added burden on the roentgenologist

A.

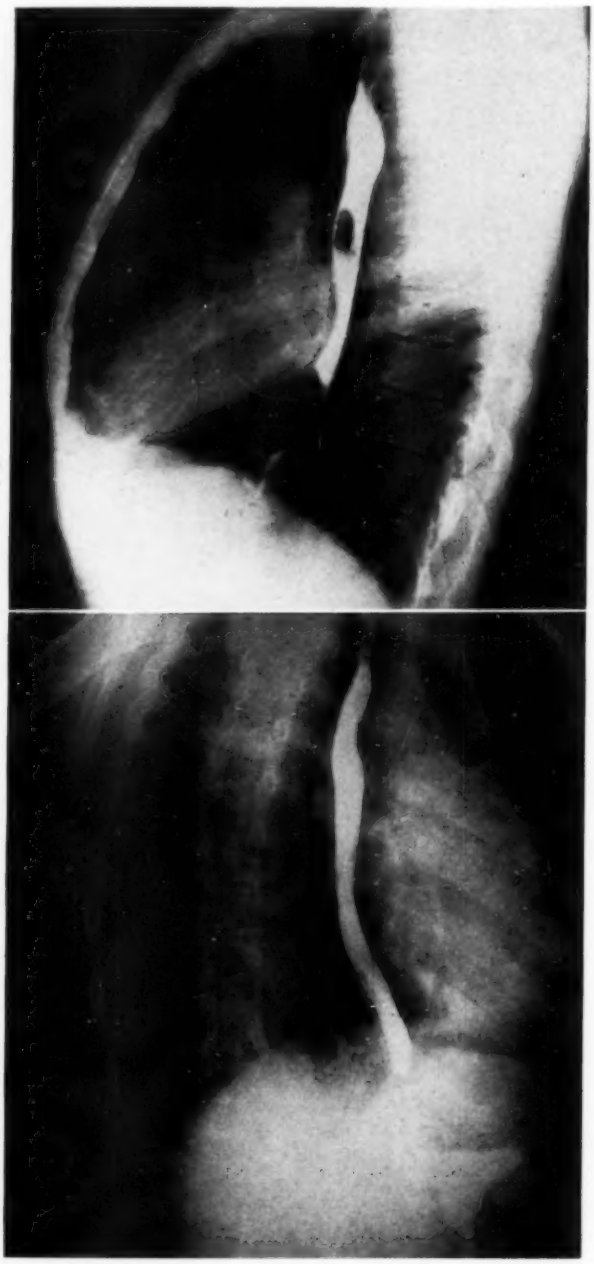


B.

Fig. 6.—Posterior enlargement of the left atrium is manifested by characteristic indentation of the esophagus in the left lateral view (*A*), while the corresponding shallow bend seen in the right oblique view (*B*) is much less diagnostic.

in terms of time and radiation exposure. Even then, oblique positioning by the technician is more subject to error and more difficult for the patient to maintain than positioning for a lateral view.

A.

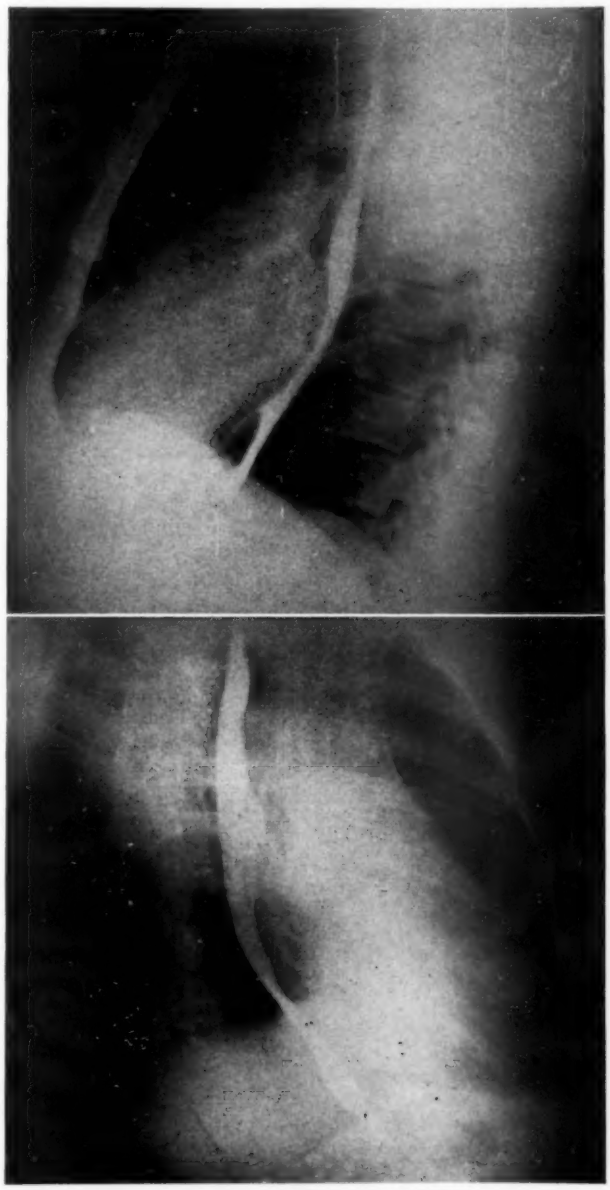


B.

Fig. 7.—Clear-cut indentation of the esophagus in the left lateral view (*A*) is seen, contrasted with the vague bend seen in the right oblique view (*B*), which is not convincing.

Finally, when economy of films dictates reduction of exposures to a minimum, two films, a posteroanterior and a left lateral chest with barium in the esophagus, should suffice for adequate roentgen examinations of the heart for

A.



B.

Fig. 8.—A distinct, well-demarcated defect of the esophageal barium column due to an enlarged left atrium is well seen in the left lateral view (*A*) but is diffuse and poorly demonstrated in the right oblique (*B*).

left atrial enlargement. In addition, any enlargement of the right ventricle can easily be appraised as it diminishes or obliterates the retrosternal space in the lateral view.

SUMMARY

In forty-nine patients with rheumatic and one with arteriosclerotic heart disease, the left lateral upright view of the chest with the esophagus opacified by barium has been found markedly superior to the right anterior oblique view in demonstrating left atrial enlargement. We feel that the left lateral view is the position of choice for evaluating left atrial size.

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"TENT-SHAPED" T WAVES OF NORMAL AMPLITUDE IN POTASSIUM INTOXICATION

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THE earliest electrocardiographic evidence of potassium intoxication is peaking of the T waves. While it has been generally considered that the T waves are tall as well as pointed, Tarail[1] noted that they need not achieve an increased amplitude. We have designated as "tent shaped" those T waves which, though of normal height, have sharp peaked tops. Such T waves were illustrated without further comment in a previous publication from this clinic.[2] Subsequently, this change has been observed in a number of patients, in some as a phase during increasing or decreasing potassium intoxication and in others as the sole electrocardiographic manifestation during a prolonged period of study. Indeed there are instances in which the recognition of this change has alerted the clinician to the incipience of potassium intoxication when there were no correlative clinical indications of its imminence. Two patients have been observed in whom failure to recognize or heed this change was, or may have been, responsible for avoidable fatalities.

The normal T wave is asymmetrical with a gradual ascending slope, a rounded summit, and an abrupt descent. An imaginary plumb line dropped from its apex forms a larger angle with the ascending than with the descending slope. The beginning of the upstroke and the end of the downstroke merge gradually with the isoelectric line. In the T waves under discussion, which may be described as tent shaped, peaked, spike shaped, or pyramidal, but of normal amplitude, the summit is sharp, and a similar imaginary plumb line forms approximately equal angles with the ascending and descending limbs. Generally the beginning of the upstroke and the end of the downstroke break abruptly with the isoelectric line.

The frequency of the occurrence of the tent-shaped T-wave change may be approximated by the fact that during the same period in which fifteen such cases were treated at the Peter Bent Brigham Hospital, eighty-one additional patients presented either tall, peaked T waves or more advanced disturbances as electrocardiographic evidence of potassium intoxication. Since the recognition of such

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a T-wave change may be a matter of extreme importance, the relevant clinical data and representative electrocardiograms of these patients are presented. These fifteen individuals have been classified arbitrarily into four groups. Group A includes patients who demonstrated either roentgenographic, electrocardiographic, or pathologic evidence of left ventricular hypertrophy. Group B consists of those with other conditions known to invert the T waves in some of the leads. Group C represents patients in whom the tent-shaped T wave was a transient phenomenon either in the progression or recession of potassium intoxication, while Group D includes patients with manifold derangements in electrolyte balance. This grouping is established in order to indicate the factors which are presumed to modify the usually expected or normal electrocardiogram.

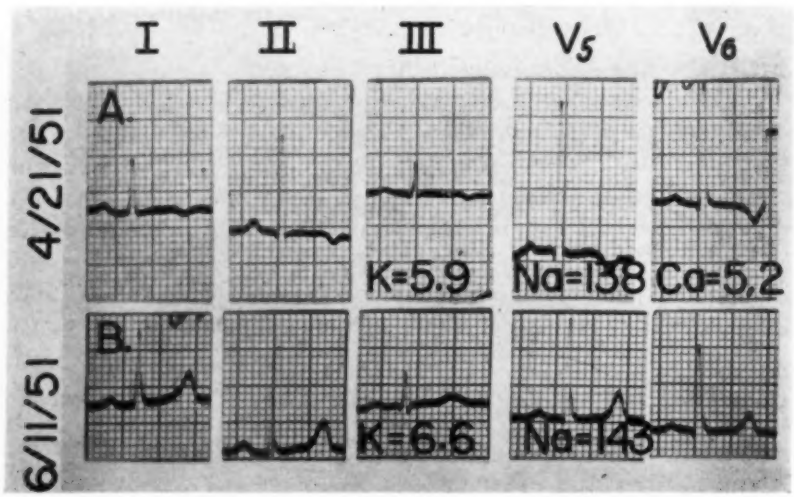

Fig 1 (Case 1).—*A*, Tracings characteristic of left ventricular hypertrophy when serum potassium was only slightly elevated. *B*, Development of tent-shaped T waves and disappearance of the pattern of left ventricular hypertrophy (Sharpey-Schafer effect) with increasing potassium level. Serum sodium and calcium levels are normal.

GROUP A. TENT-SHAPED T WAVES IN THE PRESENCE OF LEFT VENTRICULAR HYPERTROPHY

CASE 1.—A 31-year-old housewife with chronic pyelonephritis and uremia showed electrocardiograms characteristic of left ventricular hypertrophy (Fig. 1, *A*) when the serum potassium was 5.9, calcium 5.2, and sodium 138 meq. per liter, respectively.* During a subsequent admission, when two surgical procedures preparatory to renal transplanatation were done, electrocardiograms (Fig. 1, *B*) showed tent-shaped T waves. Concurrently, the serum potassium level was 6.6 and the serum sodium 143 meq. per liter.

CASE 2.—A 52-year-old woman with chronic interstitial nephritis had a unilateral nephrectomy in 1942. She then did well for about seven years but finally developed progressive renal failure. Over a long period of observation the serum potassium level was either normal or only

*All sodium and potassium values were determined by the flame photometer using the internal lithium standard. Calcium determinations were made by the method of Clark and Collip. Whenever the sample was adequate, determinations were made in duplicate.

slightly above normal. During the last few days of life the serum potassium increased to levels of 7.4 and 8.5 meq. per liter while the serum sodium dropped to 132 meq. per liter. The most extreme electrocardiographic change during this period consisted only of tent-shaped T waves. At autopsy the heart was hypertrophied.

CASE 3.—A 52-year-old man with chronic pyelonephritis, pulmonary emphysema, and hypertensive heart disease was transferred to the Peter Bent Brigham Hospital for treatment of anuria and uremia five weeks after a transurethral resection was done elsewhere for prostatic obstruction. Electrocardiograms on admission showed intraventricular block (QRS 0.11 second) and T waves which were tent shaped in all leads except Lead V_4 where they were peaked and slightly taller than normal. Serum potassium was 8.8, sodium 141, and calcium 4.2 meq. per liter. On optimal therapy his condition improved. The electrocardiograms showed disappearance of the intraventricular block and of the peaked T waves and the emergence of changes suggestive of left ventricular hypertrophy. Serum electrolytes were not redetermined when the last tracings were recorded.

CASE 4.—A 13-year-old schoolboy with chronic pyelonephritis and hypertensive heart disease was admitted to the hospital in uremia and congestive heart failure. Electrocardiograms on admission were characteristic of left ventricular hypertrophy. During his hospital stay the downhill course was complicated by the development of a *Staphylococcus aureus* septicemia and deepening uremia. Electrocardiograms now showed tent-shaped T waves with prolonged P-R (0.22 second), QRS (0.11 second), and Q-T (K= 0.54) intervals, characteristic of advanced potassium intoxication. At that time the serum potassium was 6.1 and the serum sodium 134 meq. per liter. The patient died later that day. Post-mortem examination showed chronic pyelonephritis and left ventricular hypertrophy.

These patients had in common the existence of a chronic cardiovascular renal lesion. In each, the disease was of sufficient duration and intensity to give rise to hypertrophy of the left ventricle. In no instance in this group, moreover, did the electrocardiograms, over a prolonged period of observation, ever show tall peaked T waves. A tent-shaped T wave may apparently persist in most of the leads even in the presence of more advanced electrocardiographic manifestations of potassium intoxication. This is illustrated by Cases 3 and 4. The characteristic electrocardiographic finding in left ventricular hypertrophy consists of tall R waves, depressed RS-T segments, and inverted T waves. It seems possible that this electrocardiographic effect of inverting T waves may antagonize, with more or less success, the effect of potassium in increasing the voltage of the T wave, so that tent-shaped T waves of normal amplitude rather than tall peaked T waves are observed in the presence of left ventricular hypertrophy.

GROUP B. OTHER CONDITIONS TENDING TO INVERT T WAVES (BUNDLE BRANCH BLOCK, ACUTE COR PULMONALE, AND ACUTE PERICARDITIS)

CASE 5.—A 7-year-old girl with chronic nephritis, hypertension, and uremia likewise showed tent-shaped T waves in the electrocardiogram (Fig. 2). This change was more prominent in the extremity and left lateral precordial leads (Lead V_5 unfortunately was lost in the file). The serum potassium level was 7.1 and the serum sodium 124 meq. per liter. At the time of the hyperkalemia there was a pericardial friction rub best heard along the left sternal border, and Leads V_1 to V_4 showed progressive changes very suggestive of acute pericarditis. In spite of two "runs" on the artificial kidney and decreasing chemical and electrocardiographic evidence of potassium intoxication, the urinary output decreased, and the patient developed severe acidosis and died of a massive hemorrhage from a gastric ulcer. Autopsy showed chronic glomerular nephritis, slight cardiac hypertrophy, and a hypoplastic right kidney.

CASE 6.—A 72-year-old retired locomotive engineer was admitted to the hospital because of anuria resulting from intravascular hemolysis following transurethral resection of the prostate gland. In addition to left bundle branch block, electrocardiograms recorded during the earlier part of his hospitalization (Fig. 3) showed upright, tent-shaped T waves whose direction did not seem to be predicated upon that of the QRS complexes of left bundle branch block. The additional assumption was therefore made of the presence of a complicating factor (abnormal gradient).

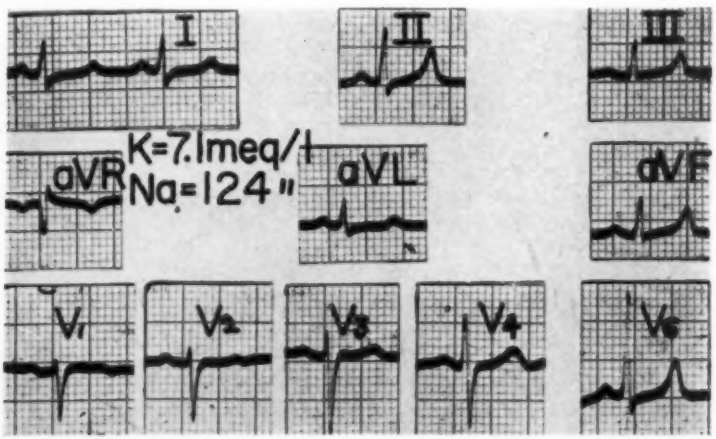

Fig. 2 (Case 5).—Tent-shaped T waves of normal amplitude are the sole electrocardiographic evidence of potassium intoxication. Note that peaking is apparent in the limb and left lateral precordial leads.

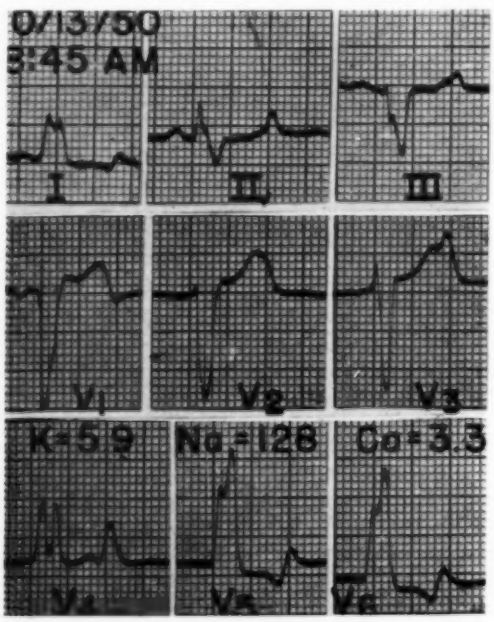

Fig. 3. (Case 6).—The tracings show characteristic QRS changes of left bundle branch block, but the direction and contour of the T waves suggest the operation of an additional myocardial factor, here suspected of being potassium intoxication.

From the configuration of these T waves the diagnosis of electrolyte imbalance was ventured. The serum potassium level at this time was 5.9, the serum sodium 128, and the serum calcium 3.3 meq. per liter. With improvement of the patient's status and change of the serum electrolytes to normal values, the electrocardiograms, though continuing to show tent-shaped T waves, took on more nearly the characteristic appearance of left bundle branch block with T waves having an opposite direction to the QRS complexes.

It has been pointed out[3] that in rare cases of potassium intoxication bundle branch block may be recorded as a phase during the development of higher grades of intraventricular block. On the other hand, in patients of this type who on continued observation fail to show greater or lesser degrees of intraventricular block, the possibility must be considered that the bundle branch block represents rather a fixed myocardial change unrelated to potassium intoxication. This was true in the present instance where the shape and direction of the T waves led to the additional assumption of potassium intoxication.

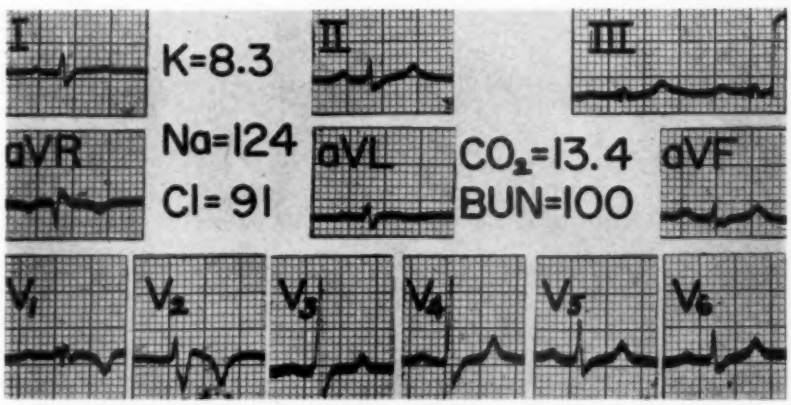

Fig. 4 (Case 7).—Tent-shaped T waves in a patient with "lower nephron syndrome" due to sulfadiazine and with poliomyelitis treated with respirator. The T waves in Leads V_1 and V_2 seem somewhat more smartly inverted than is usual with so-called "persistent juvenile pattern" of adult women and thus suggest acute cor pulmonale.

CASE 7.—A 25-year-old housewife was treated elsewhere for an acute febrile illness originally considered to be an acute septic meningitis but later proved to be acute anterior poliomyelitis. A complicating lower nephron syndrome with anuria, shock, apnea, and coma occasioned her transfer to the Peter Bent Brigham Hospital. Artificial respiration was maintained before and during the short hospital stay. The physical findings were characteristic of poliomyelitis with spinal and bulbar involvement. Electrocardiograms (Fig. 4) showed smartly inverted T waves in Leads V_1 and V_2 and tent-shaped T waves in Leads II, III, aV_F, and V_3 to V_6. These changes were considered compatible with acute cor pulmonale and potassium intoxication, though T-wave inversion in Leads V_1 and V_2 could represent the "persistent juvenile pattern" of the adult woman. Blood chemistry showed a potassium of 8.3 meq. per liter, sodium 124 meq. per liter, and a blood urea nitrogen value of 100 mg. per cent. The patient died a few hours after admission. Postmortem examination showed degeneration of the anterior horns and lateral columns of the spinal cord and lower nephron nephrosis with sulfadiazine crystals in the collecting tubules. It is suggested that the electrocardiographic signs of potassium intoxication were somehow modified by the respiratory paralysis and artificial respiration. The latter may account for the T-wave inversions over the right ventricle.

Case 12 with pericarditis, among other conditions possibly affecting the electrocardiogram, should also be listed here.

GROUP C. TENT-SHAPED T WAVES AS A PHASE DURING WAXING OR WANING OF POTASSIUM INTOXICATION

CASE 8.—A 22-year-old woman with chronic nephritis of undetermined type was admitted to the hospital because of post-partum anuria associated with pre-eclamptic toxemia and infarction of the placenta with delivery of a stillborn fetus. The clinical, chemical, and electrocardiographic findings were quite characteristic of acute renal shutdown with associated hyperkalemia. Fig. 5, *A*, which is typical of a long series of electrocardiograms recorded during the earlier part of hospitalization, shows characteristic tall, peaked T waves. At this time the serum potassium level was 5.4 and the serum sodium 136 meq. per liter. Fig. 5, *B*, recorded three days after artificial hemodialysis, at a time when the serum potassium level was actually higher (7.0 meq. per liter) and the sodium level lower (121 meq. per liter), shows tracings in which the only distinctive feature was the presence of tent-shaped T waves of normal amplitude. On further therapy the patient showed a tendency to chemical, electrocardiographic, and clinical improvement but continued to show evidence of chronic renal insufficiency.

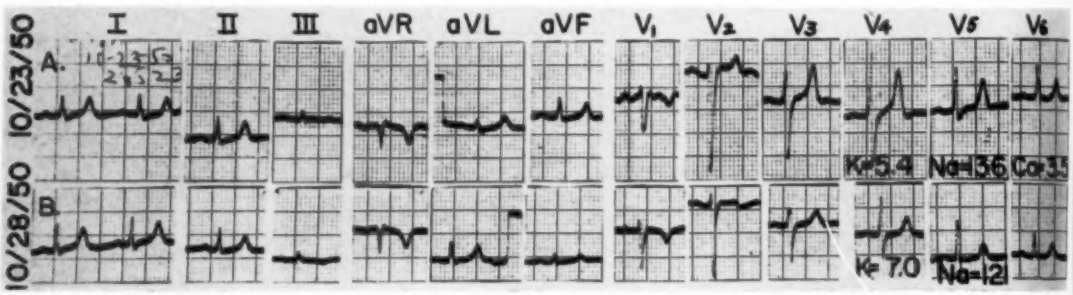

Fig. 5 (Case 8).—Tent-shaped T waves recorded as a phase during subsiding potassium intoxication. *A*, Tracing showing characteristic tall, peaked T waves before artificial kidney run. The calcium level is low, sodium slightly lower than normal, potassium only slightly increased. Note that the T waves are largest in the left precordial leads. *B*, Tent-shaped T waves recorded after kidney run. The potassium level is higher, sodium lower, calcium not determined.

In this case the normal voltage, pyramidal T waves added nothing to the diagnosis, which had already been made, but were a phase in the subsidence of electrocardiographic evidence of hyperkalemia.

In a previous publication[2] Cases 2 and 5 showed tent-shaped T waves transiently during the subsidence of more pronounced electrocardiographic evidence of potassium intoxication while Case 8 of that same report showed them during the development of more pronounced and eventually fatal potassium intoxication. These cases, as well as Case 9 of the present study, deserve inclusion here.

GROUP D. MISCELLANEOUS CASES WITH TENT-SHAPED T WAVES ASSOCIATED WITH ELECTROLYTE IMBALANCE (HYPOCALCEMIA, HYPONATREMIA) WITH OR WITHOUT HYPERKALEMIA

CASE 9.—A 30-year-old man developed hypotension, oliguria, and clinical and laboratory evidence of acute pancreatitis the day after cholecystostomy, choledochotomy, and sphincterotomy performed for common duct stones. Two days after operation, when the urinary output

was only 195 c.c., electrocardiograms showed tent-shaped T waves. At this time the serum potassium level was 4.0 and the serum sodium level 132 meq. per liter. The patient's condition continued to deteriorate. Three days later the electrocardiograms showed tall peaked T waves, and the serum potassium value rose to 7.4 meq. per liter. During the last two days of life the patient went into shock twice, each time temporarily relieved by combination therapy, consisting of intravenous calcium gluconate, sodium bicarbonate, insulin, and glucose.

At an early stage of the disease tent-shaped T waves were associated with normal serum potassium but lowered serum sodium levels. These changes, furthermore, were noted as a phase in the incipiency of electrolyte imbalance and thus constituted the first clue to the development of potassium intoxication which eventually, in whole or part, was responsible for the patient's death.

CASE 10.—A 33-year-old housewife was admitted to another hospital following the development of a hemolytic transfusion reaction associated with oliguria. While there, she developed jaundice, coma, and convulsions. The initial electrocardiograms were normal, but they subsequently showed peaking of the T waves. The serum potassium level did not rise above 4.7 meq. per liter, while the serum sodium level remained approximately 130 meq. per liter. En route to the Peter Bent Brigham Hospital for possible hemodialysis, the patient delivered a stillborn fetus.

On admission the findings were those of uremia, hematuria, hyperglycemia, hypochloremia, and anemia. The blood pressure was normal. During the first four days the electrocardiograms showed tent-shaped T waves, but otherwise they were not remarkable. At this time the serum potassium level was 4.4, sodium 126, and calcium 3.6 meq. per liter. After the correction of the hyponatremia, a diuresis occurred, and the patient began a steady course of improvement with a return of electrolytes and electrocardiogram to normal. In this patient the serum potassium was normal, and the tent-shaped T waves appeared to be associated with lowered serum sodium and calcium values.

CASE 11.—A 25-year-old housewife was admitted to the Peter Bent Brigham Hospital because of anuria of seven days' duration following a transfusion carried out during a cesarean section. The findings and course were typical of the so-called lower nephron syndrome. The patient never had an elevated blood pressure and presented no evidence of left ventricular hypertrophy. Electrocardiograms on admission were normal, but on the following day they showed tent-shaped T waves (Fig. 6), equally well seen in the chest and limb leads. Otherwise the tracings were normal. At this time the serum potassium level was 7.8, the serum sodium 128, and the serum calcium 4.3 meq. per liter. On the fifth hospital day the patient was subjected to hemodialysis. On the eighth day diuresis began and was followed by progressive clinical, chemical, and electrocardiographic improvement. Numerous repeat tracings were recorded during the three weeks of the hospitalization, but they never showed more pronounced evidence of potassium intoxication than the curves illustrated.

CASE 12.—An 18-year-old girl with chronic glomerular nephritis, hypertensive heart disease, and anemia was admitted to the hospital for treatment of uremia. The electrocardiograms on admission were characteristic of left ventricular hypertrophy. Studies of the blood chemistry showed a lowered serum calcium, elevated potassium, and lowered sodium. Appropriate therapy brought these values into the normal range, but subsequently the patient's condition deteriorated and the serum electrolytes were much as they had been on admission. Tracings taken during the following month showed at times tall, peaked T waves, at other times tent-shaped T waves with a prolonged Q-T interval. Later tracings showed an elevation of the RS-T segment suggesting pericarditis. A friction rub was heard some time later. Post-mortem examination showed chronic glomerular nephritis, hypertensive heart disease, and "uremic" pericarditis. Fig. 7, recorded when the serum potassium was 10.0, sodium 114, and calcium 3.5 meq. per liter, showed tent-shaped T waves of normal amplitude in leads related to the frontal plane of the body (Leads I, II, III, aV_F, and V_6). At this time tall, peaked T waves were not recorded. The RS-T segments were very slightly elevated in Leads I, II, aV_F, and the chest leads. In this case it is possible that

the effect of left ventricular hypertrophy, or pericarditis, or both could have been effective in antagonizing the development of tall, peaked T waves.

CASE 13.—A 14-year-old schoolboy was admitted to the hospital in a typical episode of acute glomerulonephritis which developed about three weeks after an attack of acute pharyngitis. During the first four days of hospitalization, the daily urinary output never exceeded 150 c.c.,

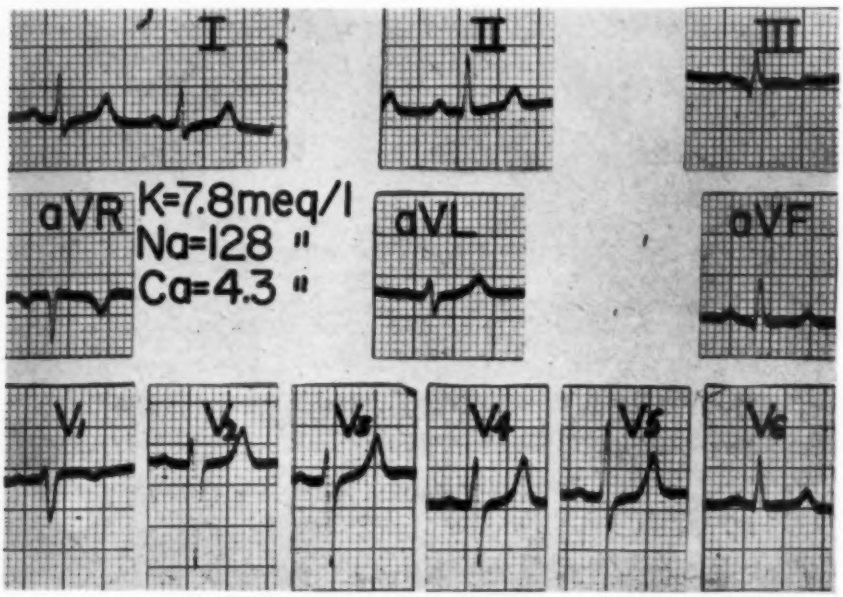

Fig. 6 (Case 11).—Tent-shaped T waves of normal amplitude are the sole electrocardiographic manifestation of potassium intoxication. Note that the ascending and descending limbs of the T waves have an approximately equal slope, that the beginning and ends of the T waves break abruptly with the isoelectric line, and that the summits of the T waves are sharp.

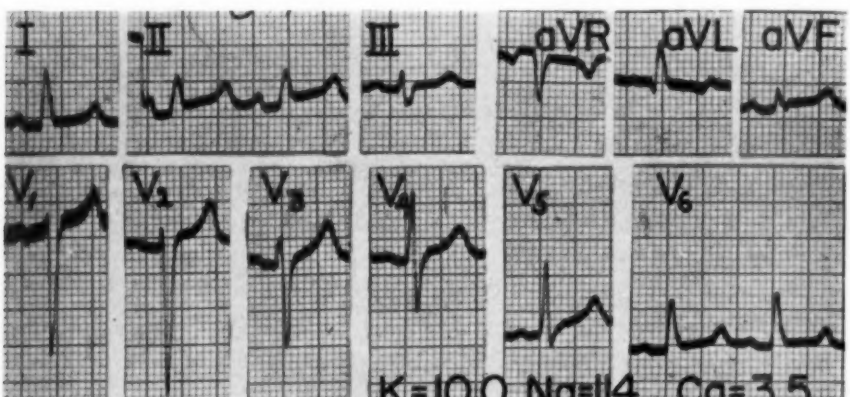

Fig. 7 (Case 12).—Tracings recorded in a girl with hypertensive heart disease and uremia with hyperkalemia, hyponatremia, and hypocalcemia. Note the tent-shaped T waves especially in Lead V_6 and elevation of the RS-T segments in Leads I, II, aV_F, and V_2 to V_6, suggesting pericarditis, which was subsequently confirmed clinically and pathologically.

and on the fifth and sixth days he was totally anuric. The patient had an elevated blood pressure but showed no clinical or roentgenologic evidence of left ventricular hypertrophy. A tracing taken on the third hospital day showed tent-shaped T waves at the upper limits of normal height. There were no other electrocardiographic stigmas of potassium intoxication. At that time the serum potassium level was 7.6 and the serum sodium level 131 meq. per liter. On the fourth hospital day tent-shaped T waves were still present which were not quite as tall in Lead V_2 but of the same height elsewhere (Fig. 8). At this time the serum potassium level was 8.6 meq. per liter. These tracings were quite representative of a series of electrocardiograms taken daily during the first week of hospitalization when the serum potassium level ranged between 7.3 and 8.7 meq. per liter and the sodium level between 129 and 135 meq. per liter. Upon subsequent diuresis the serum electrolytes became normal, and the T waves returned to a substantially normal appearance.

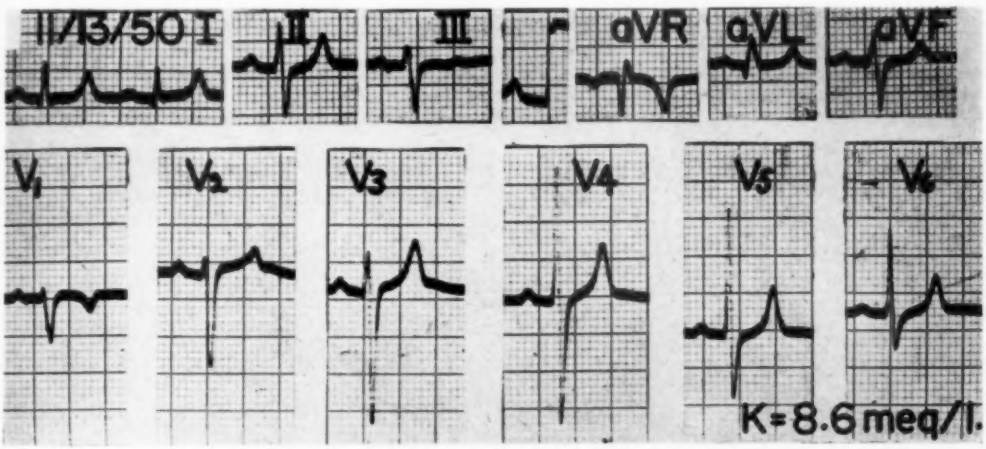

Fig. 8 (Case 13).—Tent-shaped T waves at the upper limits of normal height in potassium intoxication. Note that the T waves are somewhat taller in the chest than in the extremity leads.

In this case then pyramidal T waves of normal amplitude were again the only distinctive electrocardiographic finding to suggest potassium intoxication.

Recent work has established that potassium-depleting procedures or conditions, which are often encountered clinically, produce or enhance digitalis toxicity in digitalized patients.[4,5] This, together with the well-substantiated fact that the administration of potassium salts can promptly eliminate premature ventricular beats, may impel the injudicious use of these salts.[5,6] The following two cases are presented to illustrate the real risk of potassium administration in the presence of either severe congestive failure or oliguria as well as the importance of recognizing tent-shaped T waves in the anticipation of hyperkalemia.

CASE 14.—A 72-year-old woman with coronary and hypertensive heart disease and chronic auricular fibrillation was admitted to another hospital for treatment of congestive heart failure. Electrocardiograms on admission showed left ventricular hypertrophy, multifocal ventricular premature beats, and bidirectional ventricular tachycardia (Fig. 9, *A*). This pattern persisted despite the cessation of digitalis for over four weeks. In order to obviate the extrasystoles, she received 10 Gm. of potassium chloride orally. This was followed within two hours by the disappearance of all premature beats and the development of tent-shaped T waves (Fig. 9, *B*). But the potassium effect was transient, and within six hours extrasystoles returned. A few weeks later, because of advancing congestive failure and increasing evidence of myocardial irritability manifested by brief outbursts of ventricular tachycardia and runs of bidirectional ventricular

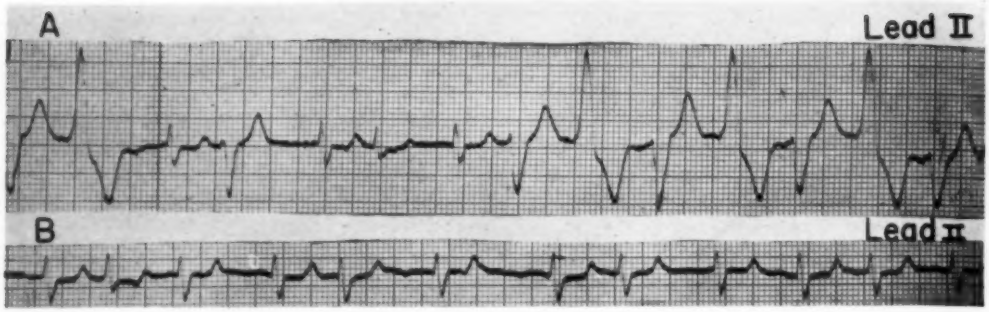

Fig. 9 (Case 14).—*A*, Lead II recorded in a 72-year-old woman with coronary and hypertensive heart disease and auricular fibrillation, showing multifocal ventricular premature beats. *B*, Same after 10 Gm. of potassium chloride by mouth showing disappearance of ventricular premature beats and development of tent-shaped T waves.

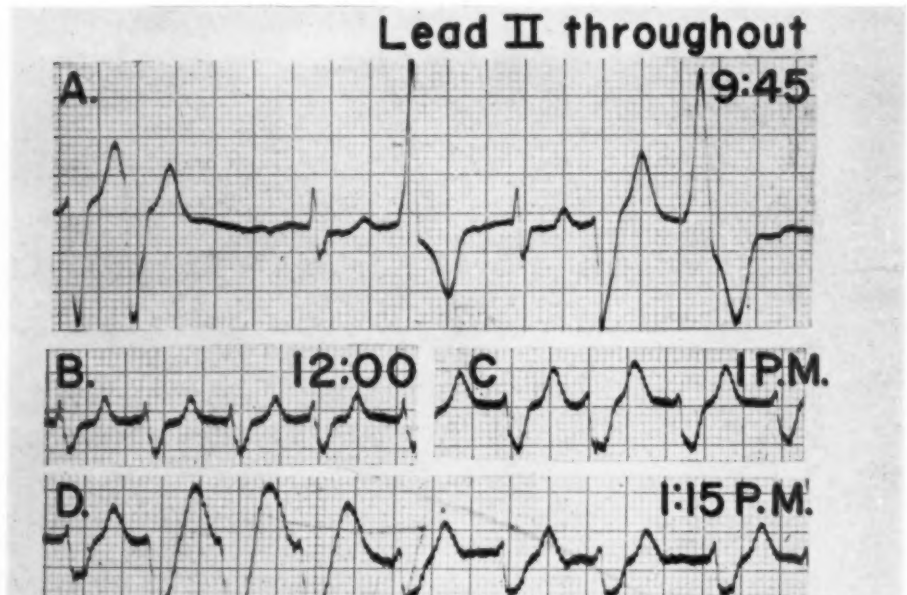

Fig. 10 (Case 14).—Fatal potassium intoxication. *A*, Redevelopment of multifocal premature ventricular beats; *B*, two hours after 15 Gm. of potassium chloride by mouth showing development of intraventricular block and tent-shaped T waves; *C*, one hour later, increasing intraventricular block; *D*, fifteen minutes later, further deterioration of the ventricular complex, ventricular slowing, and an ectopic rhythm, probably a short paroxysm of ventricular tachycardia; *E*, three minutes later, terminal ventricular fibrillation.

tachycardia, a larger dose of potassium chloride was administered prior to a planned digitalization. The urea clearance and serum electrolytes were normal. The tent-shaped T waves which developed at the previous potassium administration were not recognized as evidence of hyperkalemia. She received 15 Gm. of potassium chloride orally. An electrocardiogram prior to the potassium ingestion is shown in Fig. 10, *A*. Two hours later she showed tent-shaped T waves (Fig. 10, *B*). Again the significance of this change was not appreciated. The potassium at this time, as subsequently determined, was 7.8 meq. per liter. Despite appropriate therapy there followed a progressive deterioration of the electrocardiogram with increasing intraventricular block at three hours (Fig. 10, *C*), ventricular slowing and ectopic rhythm, probably short paroxysms of ventricular tachycardia, at three hours and fifteen minutes (Fig. 10 *D*), and terminally ventricular fibrillation at three hours and eighteen minutes (Fig. 10, *E*).

CASE 15.—A 52-year-old woman with rheumatic heart disease, auricular fibrillation, and congestive heart failure was admitted for mitral valvuloplasty. Several electrocardiograms taken before operation showed auricular fibrillation, digitalis effect, left ventricular hypertrophy, and ventricular premature beats, occasionally repetitive and occasionally bigeminal and therefore regarded as very suggestive of digitalis intoxication. On the first postoperative day, because of the recurrence of bigeminal rhythm, the patient was given 5 Gm. of potassium chloride by vein. On the following day electrocardiograms showed right bundle branch block and tent-shaped T waves in Leads I, II, and aV_L interpreted as suggesting potassium intoxication. Leads V_4 to V_6 could not be recorded because of the operative dressing. A serum potassium level was not determined at this time. That evening the patient developed an obscure and unexplained episode of somnolence, unresponsiveness, respiratory distress, and circulatory collapse from which she recovered. This episode was attributed to acute pulmonary embolism. On subsequent diuresis the tent-shaped T waves disappeared. The patient died several days after operation. Autopsy showed advanced rheumatic endocarditis, early pneumonia, and purulent bronchitis.

In Case 15 oral potassium induced the transient collapse, while in Case 14 it was the immediate cause of the fatal outcome. In each case the tent-shaped T wave which foreshadowed the eventual catastrophe was not appreciated. It is not well recognized that in congestive failure there is an impaired excretion of ingested potassium.[8] The utilization of large doses of potassium salts in such patients to eliminate the signs of digitalis overdosage is hazardous. In effect one leaps from the frying pan of digitalis intoxication into the fire of potassium poisoning.

COMMENT

Anatomical and Physiological Antagonisms to the Development of Tall, Peaked T Waves.—It is not known why some patients with potassium intoxication develop tall, peaked T waves while others show tent-shaped T waves of normal amplitude. Langendorf and Pirani[9] regard the electrocardiogram in uremia as the composite effect of certain factors, some of which may produce effects in one direction while others may produce effects in an opposite direction. These effects may thus balance or obscure one another. It is clear from the very manner and order of this presentation that the present authors share this view. It has been observed repeatedly in this clinic in patients with left ventricular hypertrophy that during the development of potassium intoxication the electrocardiograms may show sequential changes from one characteristic of left ventricular hypertrophy with inverted T waves over the left ventricle, through an intermediate phase with sharp but small upright T waves in the same region, to one characteristic of potassium intoxication with tall, peaked, upright T waves.

This phenomenon was first observed by Sharpey-Schafer[10] and is well illustrated in Fig. 10 of a previous publication.[2] During the recession of potassium intoxication the reverse of this process has also been observed. If the forces tending to produce tall T waves were strong enough, the low voltage peaked T waves might, as in Cases 8 and 9 of the present study and Cases 2 and 5 of the previous one, be recorded merely as a transient phenomenon. On the other hand, if the forces responsible for an upright T wave were more nearly in balance with those of hypertrophy, which tends to invert the T waves, then these tent-shaped T waves might be recorded over a prolonged period. This concept could account, in whole or part, for the changes in Cases 2 and 3 and for the failure to develop tall T waves in left bundle branch block (Case 6), acute pericarditis (Cases 5 and 12), or acute cor pulmonale (Case 7), conditions which have in common with ventricular hypertrophy the electrical effect of inverting the T waves in certain leads or combination of leads.

Topographical Antagonism to the Development of Tall, Peaked T Waves.—It was first observed by Finch and associates[11] that in potassium intoxication tall, peaked T waves are apt to be most prominent in the precordial leads. At the same time the T waves in the limb leads might appear normal or peaked but of low voltage. This phenomenon has been observed repeatedly since that publication. There are some rare instances in which the T waves may be taller in the limb than in the chest leads or taller in leads recording changes referable to the frontal as contrasted with the sagittal plane of the body (Fig. 2). These considerations suggest that the abnormal T-wave vector has generally a much larger area of projection upon the chest than upon the extremity leads and, therefore, while its projection upon the chest leads may be tall and peaked, that upon the extremity leads may be lower and tent shaped. If the plane of the spatial T-wave vector happens to lie somewhere between these two planes, its projection upon either of them might approximate or equal a tent shape. The fact that in some of our cases the T wave, as recorded at certain points, might at one time be tall and peaked and at other times tent shaped suggests that the spatial orientation of the T-wave vector may change from time to time. It is anticipated that the new techniques of vectorcardiography may clarify this aspect of the problem.

Concomitant Electrolyte Derangements Modifying the Electrocardiogram of "Potassium Intoxication."—The general conception of the relationship between the electrocardiogram and potassium poisoning has changed considerably during the past decade. Opinion has varied from the simple assumption of a linear relationship between serum potassium level and electrocardiographic appearance[12] to the opposite view that there is no relationship between the two.[13,14] It has been demonstrated[2] that the serum sodium level has a pronounced influence upon the effect of a given potassium level; normal serum sodium antagonizes and decreased serum sodium level enhances the effect of potassium in producing an abnormal electrocardiogram. More recently, a similar relationship has been found[15] between serum calcium level and potassium poisoning, normal calcium likewise antagonizing and decreased calcium enhancing the deleterious electrocardiographic effects of potassium. These represent in effect clinical counter-

parts of the classical experimental observations of Ringer.[16] The possible role of other electrolytes, such as phosphate and magnesium, remains to be investigated. The brilliant studies of Darrow[12] have demonstrated that changes in extracellular fluids alter the electrolyte content of cells and conversely that the composition of the cells leads to changes in the extracellular fluids. The interrelationships are complex. It is clearly difficult, if not impossible, to produce or observe an isolated change in one of the serum electrolytes without producing or observing concomitant changes in other extracellular, or, indeed, in other intracellular, electrolytes. Most of the cases here presented had an elevated serum potassium level. In most of these the hyperkalemia was associated with hyponatremia (Cases 2,3,5,7,8,11, and 13) and, in the case in which calcium was measured, with hypocalcemia as well (Case 6). There were two cases in this group in which the serum potassium level was normal, but in which the sodium (Case 9) or the sodium and calcium levels (Case 10) were depressed. In the tracings published by Levine[17] and by Ernstene and Proudfit[18] from single cases of hypocalcemia, the T waves were tent shaped. It seems possible then that elevated serum potassium, lowered calcium, or lowered sodium, alone or in concert, appear to be capable of producing the electrocardiographic appearance which we have designated as a variant of "potassium intoxication."

T waves of this form have also been described by Alzamora-Castro and coworkers[19] as one of the varieties of abnormal but upright T waves occurring in the presence of myocardial disease. It is clear then that tent-shaped T waves do not necessarily indicate hyperkalemia in particular or electrolyte changes in general. In our experience, admittedly influenced by a disproportionate selection of patients with acute or chronic renal failure, referred to this hospital for treatment with the artificial kidney, we found that potassium intoxication is by far the most frequent underlying cause. The wary physician is urged to be on the alert for this finding.

SUMMARY AND CONCLUSION

1. Certain individuals may show as the earliest, or as the sole, electrocardiographic evidence of potassium intoxication tent-shaped T waves of normal amplitude rather than tall, peaked T waves.

2. In some instances this change is observed transiently during increasing or subsiding potassium intoxication. In others it remains as a constant finding over a prolonged period of observation.

3. This finding is not necessarily associated with electrolyte changes, but it is generally correlated with an elevated serum potassium level and, in most cases, with a simultaneously lowered serum sodium level. Rarely it may be detected with a normal serum potassium level but with lowered values of sodium, or of calcium, or of both.

4. This change may conceivably result from the concomitant operation of certain anatomical-electrical effects, like left ventricular hypertrophy, bundle branch block, pericarditis, or acute cor pulmonale. These conditions have in common the electrical effect of inverting T waves and thus possibly of opposing the effect of potassium in making T waves upright and tall.

5. Tent-shaped T waves may, in certain instances, result from the diminutive projection of the abnormal T-wave vector upon certain planes of the body.

6. Regardless of its mechanism it is a change which should not pass unrecognized, for these individuals are prone to the danger of cardiac standstill which besets individuals with potassium intoxication.

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THE USE OF ORAL QUINIDINE AND PROCAINE AMIDE AS PREMEDICATIONS FOR CARDIAC CATHETERIZATION

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THIS report is concerned with the need for prophylactic measures to reduce the incidence of potentially dangerous arrhythmias induced during cardiac catheterization. The experience of this catheterization team will be presented, and suggestions for increasing the safety of routine cardiac catheterizations will be made.

INTRODUCTION

With the rapid and widespread development of the cardiac catheterization technique as an aid to diagnosis and a tool for physiologic research, increasing numbers of these procedures will be done under less than ideal conditions. With the rapid advances in cardiac surgery careful exploration of the cardiac chambers for transposed pulmonary veins and septal defects will increase the amount of direct probing of the endocardium with the catheter tip. If any measures may be taken to reduce the irritability of the myocardium to direct catheter stimuli, they will be of great importance not only in reducing the hazards of the procedure, but in permitting adequately detailed study to reveal surgically correctable anomalies. The report of Goldman and associates, in February, 1950,[1] emphasized the need for measures to interrupt major rhythmic disturbances once they had occurred. The present study is an evaluation of prophylactic medication used during the past three years in preparing patients for cardiac catheterization.

MATERIAL AND METHOD

In the course of 161 cardiac catheterizations at the Los Angeles County General Hospital, sufficient data were found in 113 cases to estimate the severity of the procedure, the types of arrhythmia induced, and the premedication used. The procedure was subjectively graded as severe, moderate, or minimal on four criteria: First, the amount of manipulation required to pass the tricuspid and

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pulmonic valves was noted. Second, the time spent searching atrial and ventricular walls and septa for anomalies was estimated. Third, the number of catheters withdrawn and inserted was determined. Fourth, the total duration of the procedure was recorded. Continuous direct-writer electrocardiographic records were taken throughout the cardiac catheterization and served as the basis for evaluation of the arrhythmias. The term, major arrhythmia, includes all instances where more than three short runs (three to six beats) of ventricular tachycardia, any prolonged tachycardia other than those of sinus origin, or any persistent bundle branch block appeared. Minor arrhythmias included occasional premature contractions of any origin, or three or less short bursts of ventricular tachycardia. These two classes were mutually exclusive. Finally the hospital records were reviewed for cardiac premedication, if any. No association of these three variables, severity of procedure, severity of arrhythmia, and cardiac premedication, was made until the data on each were independently obtained. This "blind" technique excluded any bias which might otherwise occur in the evaluation of a subjective variable.

RESULTS

For some time either we used no premedication, or we used oral doses of 0.2 Gm. of quinidine at three- to four-hour intervals four to six times prior to the procedure. A clinical impression was obtained that such doses were no better than no medication in controlling arrhythmias stimulated by the catheter.

Quinidine was then arbitrarily administered two hours prior to and immediately preceding catheterization in doses of 10 mg. per kilogram of body weight, as most likely to permit an adequate drug level, not only at the beginning, but throughout the cardiac catheterization procedure. These doses approximate the values found to be most often effective by Houston and Perry[5] in their correlation of blood levels with dosages related to body weight. Procaine amide was alternately used in the same dosage on the basis of its known action.[3]

TABLE I.

CATHETER-INDUCED IRRITATION		MAJOR ARRHYTHMIAS			MINOR ARRHYTHMIAS		
		SEVERE	MODERATE	MINIMAL	SEVERE	MODERATE	MINIMAL
10 mg. per kilogram every two hours × two	Quinidine	5	2	0	6	11	7
	Procaine amide	5	2	1	4	10	4
Less than 10 mg. per kilogram	Quinidine	8	8	7	7	5	3
	Procaine amide	0	3	0	0	1	0
No premedication		2	3	1	4	2	2

It will be seen from Table I that fifty-seven patients received the larger dosage schedule, while fifty-six patients had no cardiac premedication, or quini-

dine, or procaine amide in amounts less than 10 mg. per kilogram of body weight. Severe irritation was noted in 35 per cent of the catheterization procedures preceded by 10 mg. per kilogram doses and in 37.5 per cent of the others. Moderate procedures comprised 44 per cent of the large dose group and 39.5 per cent of the group receiving less than 10 mg. per kilogram. Of the 10 mg. per kilogram group, 21 per cent had minimal trauma as opposed to 23 per cent of the group receiving lesser medication. As the two groups were equal in number and similar in distribution of relatively difficult, moderate, or easy catheterizations, they can be suitably compared with respect to the effect of medication on the arrhythmias.

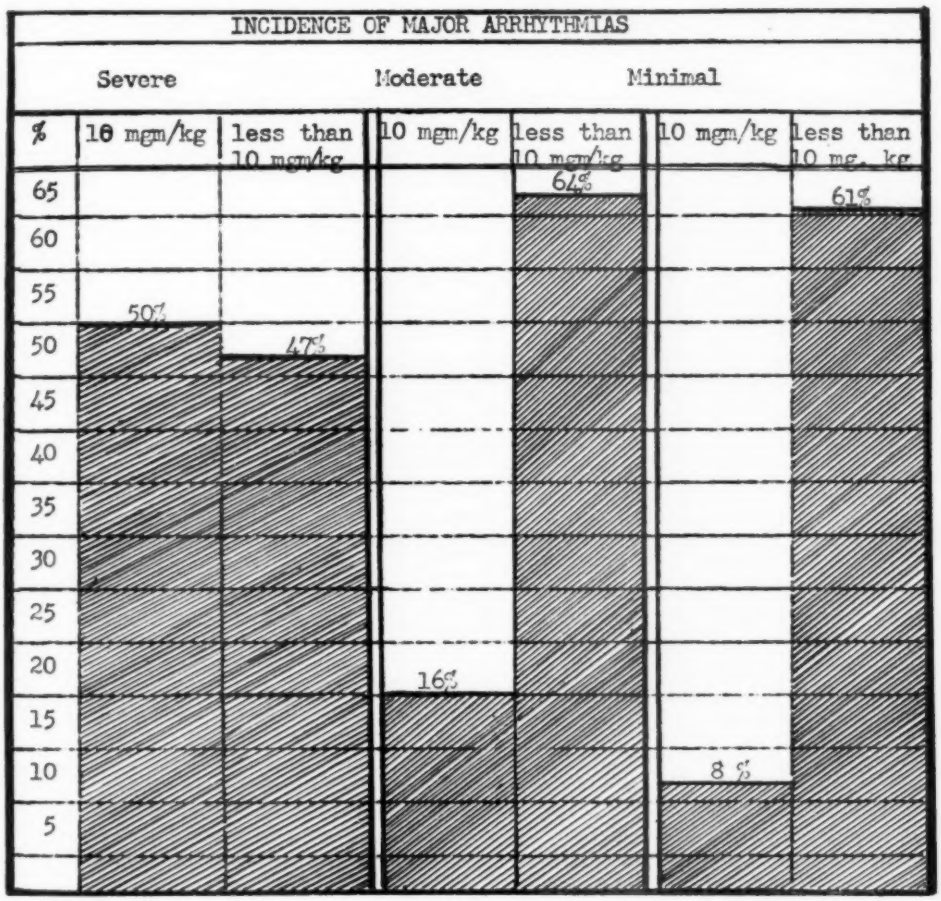

Fig. 1.

Fig. 1 graphically demonstrates that quinidine and procaine amide premedications in the larger doses suppress the production of major arrhythmias incident to the passage of the catheter, provided severe irritation is not induced. In the severe group, the prolonged probing with the catheter tip induced as many major arrhythmias in the one group as in the other.

Fig. 2 shows three charts (*A*, *B*, and *C*) relating the amount of premedication to the severity of the arrhythmia in each of the three subjectively determined groups representing catheter-induced myocardial irritation. Direct determination of the probability of chance association producing the findings in each group was calculated from the binomial distribution of twofold occurrences according to Fisher.[7] Medication had no demonstrable influence in the group severely irritated by the catheter (Fig. 2,*A*). In those receiving moderate catheter irritation, 10 mg. per kilogram doses were more effective in preventing major arrhythmias than were lesser doses (Fig. 2,*B*). P equaled 0.001 in this group, allowing a high degree of significance to be attributed to these findings. In the minimally irritated patients, the larger premedication dosage schedule also produced significant suppression of major arrhythmias (Fig. 2,*C*). P here was 0.01.

A

	Major Arrhythmia	Minor Arrhythmia
10 mg. per kg.	a: 10	b: 10
Less than 10 mg. per kg.	c: 10	d: 11

Severe procedures
P = 0.4

B

	Major Arrhythmia	Minor Arrhythmia
10 mg. per kg.	a: 4	b: 21
Less than 10 mg. per kg.	c: 14	d: 8

Moderate procedures
P = 0.001

C

	Major Arrhythmia	Minor Arrhythmia
10 mg. per kg.	a: 1	b: 11
Less than 10 mg. per kg.	c: 8	d: 5

Minimal procedures
P = 0.01

D

	Major Arrhythmia	Minor Arrhythmia
Quinidine 10 mg. per kg.	a: 2	b: 18
Procaine amide 10 mg. per kg.	c: 3	d: 14

Moderate and minimal procedures
P = 0.3

Fig. 2.

In preventing arrhythmias, quinidine was no more effective than procaine amide when given according to the 10 mg. per kilogram schedule, as far as can be determined from the small numbers involved (Fig. 2,*D*).

CONCLUSIONS

1. When the irritation is moderate or minimal, both quinidine and procaine amide in doses of 10 mg. per kilogram of body weight decrease significantly the incidence of catheter-induced auricular, nodal, or ventricular tachycardias, as well as persistent bundle branch blocks.

2. This premedication is of no value if the catheter-induced irritation is marked. Manipulation of the catheter must be as gentle as possible.

3. Routine use of these premedications in cardiac catheterization will permit safer procedures and more adequate studies.

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ELECTROCARDIOGRAPHIC CHANGES UNDER EMETINE THERAPY*

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THE electrocardiographic studies so far performed in patients under emetine therapy have been based on standard leads and only one precordial lead. Hardgrove and Smith[1] have reported only minor electrocardiographic changes in cases treated with emetine. Heilig and Visveswar[2] did not find noteworthy alterations in patients who received up to a total of 0.72 Gm. of emetine (0.06 Gm. daily). Levy and Rowntree[3] reported in 1916 that excessive doses of emetine produced ventricular fibrillation in rabbits. Boyd and Scherf[4] have studied the electrocardiographic changes in patients under acute emetine intoxication and have found no significant alterations of the T wave. However, when a high dosage was reached, they observed disturbances in the atrioventricular and interventricular conductions and auricular and ventricular extrasystoles. Klatskin and Friedman[5] have reported electrocardiographic changes in 52.7 per cent of a series of cases treated with emetine.

MATERIAL AND METHODS

A group of forty-five patients with amebiasis (most of them with liver abscess), between the ages of 15 and 40 years, without any history of cardiovascular disease was selected from the Medical and Surgical wards of the Hospital General (Mexico City). The drug chosen for this study was emetine hydrochloride,† and the route of administration was intramuscular. Electrocardiographic control tracings were taken in all patients, then every three or four days during the treatment, and at intervals of eight to ten days after the drug was discontinued until the disappearance of the electrocardiographic alterations. Due to difficulties in contacting the patients, a complete follow-up was done in only eight of the forty-five patients.

The electrocardiograms taken included the three standard leads, the augmented unipolar limb leads, and six precordial V leads.

RESULTS

P.—No P-wave changes were observed.

P-R.—The P-R interval was prolonged in two of the forty-five patients. One showed a P-R of 0.22 second and the other of 0.23 second. The atrio-

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ventricular block in the latter disappeared on the thirty-second day after emetine was suspended.

ÂP.—ÂP showed a left deviation in 18 per cent of the cases and a right deviation in 18 per cent, while in the remaining no ÂP deviation was observed.

QRS.—No significant changes were observed in the QRS complex.

ÂQRS.—In 62 per cent of the cases the ÂQRS showed a right deviation (average 18 degrees) and a left deviation in 37 per cent of the cases (average 28 degrees). No important changes were seen in voltage.

ÂT.—ÂT showed a right deviation of 25 degrees (average) in 27 per cent of the cases and a left deviation of 44 degrees (average) in 72 per cent of the cases. In one of the patients with right axis deviation there was a decrease in voltage of 4.5 mv. seconds. In 50 per cent of those that presented a left deviation, there was found a reduction of voltage of 10.0 mv. seconds.

Ĝ.—The ventricular gradient showed a deviation to the right in 36 per cent of the cases (average 20 degrees); in 36 per cent of the series there was an average left deviation of 29.7 degrees; the rest did not present any changes. Concerning the voltage of the gradient, of those who showed a right deviation, there were only two who presented a decrease, one of 7.5 and the other of 5.5 mv. seconds. In those patients with deviation to the left, one showed a reduction of 21.0 and another of 23.5 mv. seconds, while a third one presented an increase of 14.5 mv. seconds. The remainder did not reveal significant changes (Table I).

TABLE I.

Deviation of ÂQRS toward	the right in 62 per cent, average 18 degrees
	the left in 37 per cent, average 28 degrees
Deviation of ÂT toward	the right in 27 per cent, average 25 degrees
	the left in 72 per cent, average 44 degrees
Deviation of Ĝ toward	the right in 36 per cent, average 20 degrees
	the left in 36 per cent, average 29.7 degrees

S-T.—There was an S-T upward shift of no more than 1.0 mm. (bowed in shape) in the standard leads in 18 per cent of the cases, with an average total dose of 0.015 Gm. per kilogram of body weight which disappeared about sixteen days after the emetine was suspended. In the precordial leads this shift appeared in 45 per cent of the cases approximately fifteen days after emetine was started, with an average total dose of 0.014 Gm. per kilogram of body weight. These changes disappeared about forty-one days after treatment (Table II).

T.—The earliest and outstanding electrocardiographic change was seen in the T wave. In Leads I and II the T appeared inverted in 18 per cent of the cases with an average total dose of 0.012 Gm. per kilogram of body weight. An average time of seven weeks was required for the return to normal of this wave. In the precordial leads (V_1 to V_6) the inversion of T occurred in all cases

(100 per cent). The change started with an average total dose of 0.011 Gm. per kilogram of body weight, seven days after the onset of emetine therapy, and disappeared between nine days and three and one-half months later (average fifty-three days) (Table II).

TABLE II.

		PERCENTAGE	AVERAGE TOTAL DOSE PER KILOGRAM OF BODY WEIGHT	AVERAGE TIME FOR DISAPPEARANCE OF CHANGES AFTER THE END OF THERAPY (DAYS)
S-T Elevation	Standard leads	18	0.015	16
	Precordial leads	45	0.014	41
T Inversion	Standard leads	18	0.012	51
	Precordial leads	100	0.011	53
Q-T Prolongation		90	0.020	50

Q-T.—The electrical systole was prolonged by the drug in 90 per cent of the series. This change appeared with an average total dose of 0.02 Gm. per kilogram of body weight and disappeared in an average lapse of 50 days (Table II).

All the electrocardiographic changes described were reversible (Figs. 1 to 15).

One of the patients under study received, through an oversight, a total dose of 1.50 Gm. of emetine (0.10 Gm. daily) and presented the expected signs of intoxication: a drop in blood pressure, abolition of tendon reflexes, marked asthenia, and adynamia, as well as electrocardiographic changes (Figs. 16 to 18). The patient died several days later from a superimposed pneumonia. A histopathological study was performed.* Following are the results:

"*Heart*: The heart is pale in color and flabby in consistency. The fibers of the myocardium are broad and striated but unevenly stained (hematoxylin-eosin). The capillaries are engorged. There are scattered areas of leukocytic infiltration (mainly mononuclear cells). Diagnosis: Acute myocardial degeneration. Compatible with emetine intoxication" (Fig. 19).

"*Liver*: There are no gross noteworthy changes. The microscopic examination discloses a slight diffuse infiltration of fat. The liver cells reveal a marked difference in the size of their nuclei. Some of the hepatocytes show deposits of a golden-yellow pigment. The portal spaces and the sinuses contain a large number of round cells. Diagnosis: Fatty degeneration of no specific etiology" (Fig. 20).

"*Kidney*: The kidneys are grossly normal. There is a passive congestion of the medular zone. Diagnosis: The findings may be due to agonal changes" (Fig. 21).

DISCUSSION

Electrocardiographic study is of utmost importance in patients undergoing emetine therapy since it permits the detection of early action of the drug as well as the time when such action disappears.

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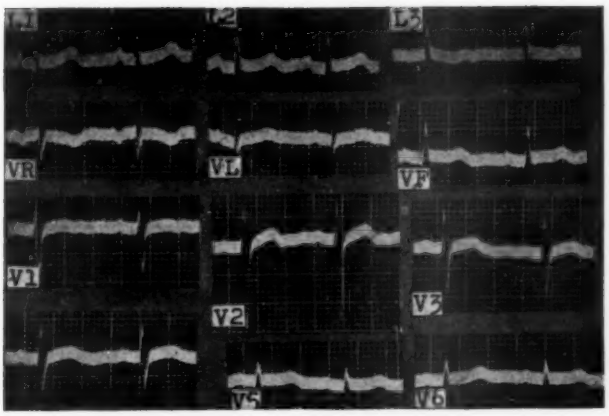

Fig. 1.—Patient A. T. Control tracing; normal record (June 24, 1947).

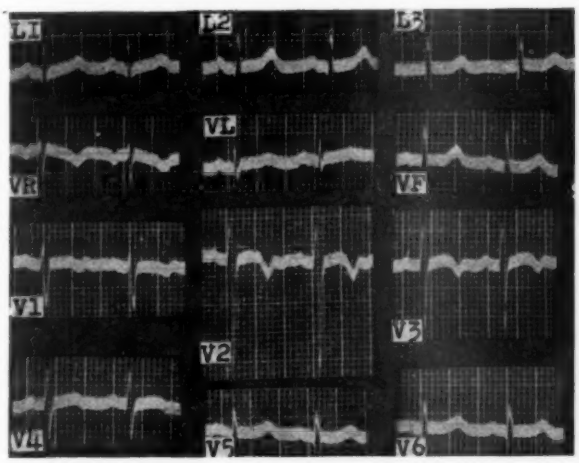

Fig. 2.—Patient A. T. The second record, taken after a total dose of 0.60 Gm. (0.05 Gm. daily). T is inverted in V_1, V_2, and V_3. Q-T is normal (July 7, 1947).

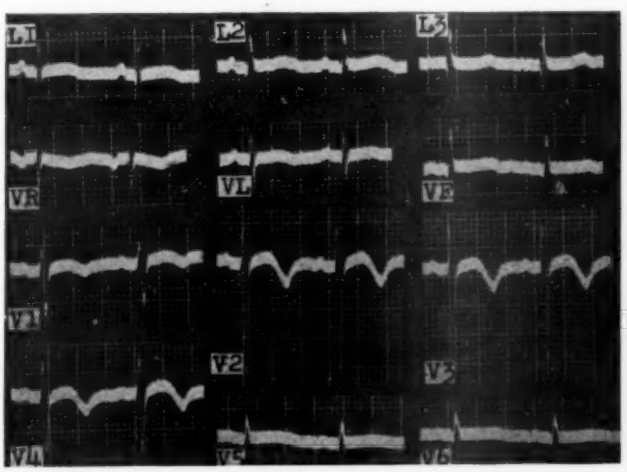

Fig. 3.—Patient A. T. The third tracing, taken after a total dose of 0.90 Gm. T is more inverted. S-T starts to show an upward shift, a tendency to low voltage. Q-T: M.V. + 0.09 second (July 16, 1947).

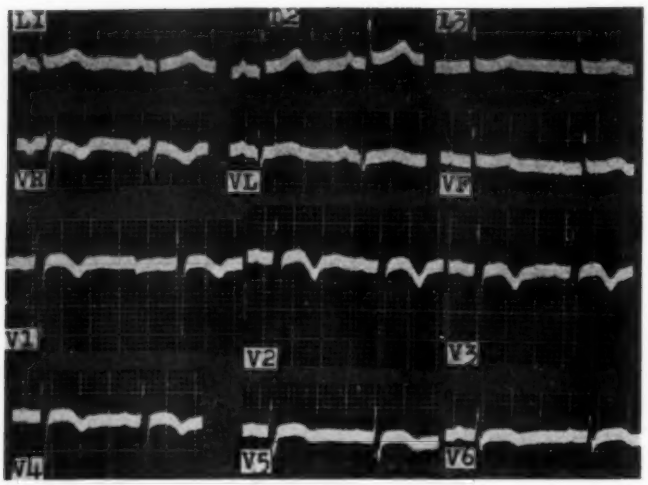

Fig. 4.—Patient A. T. The fourth tracing, taken sixteen days after emetine was discontinued. Electrocardiographic changes tend to disappear. Q-T is now normal (Aug. 2, 1947).

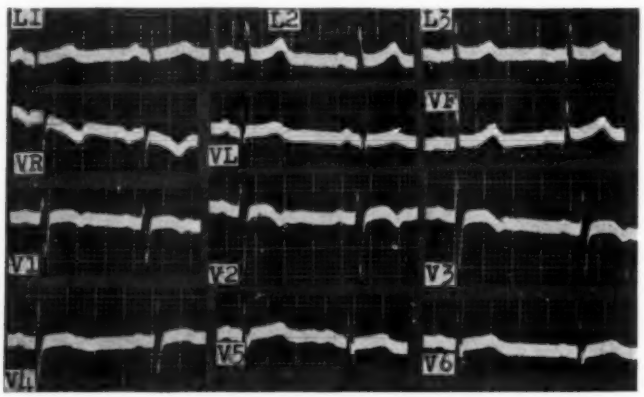

Fig. 5.—Patient A. T. The fifth tracing, taken thirty-one days after cessation of treatment. T has become positive in V_4, less inverted in the remaining precordial leads (Aug. 15, 1947).

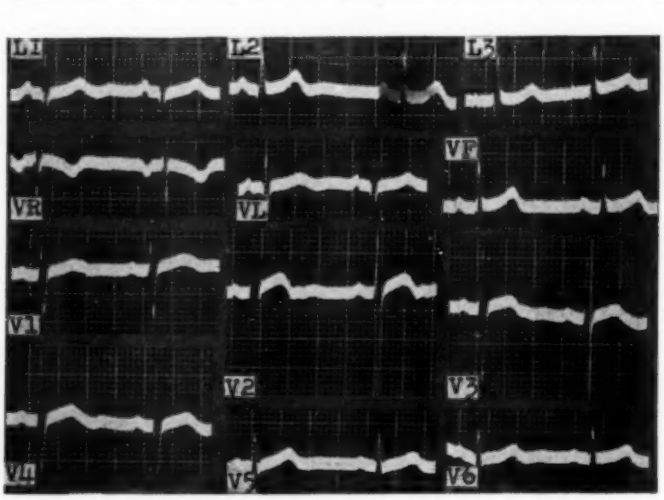

Fig. 6.—Patient A. T. The sixth (and last) tracing, taken sixty-seven days after treatment. The electrocardiogram is normal.

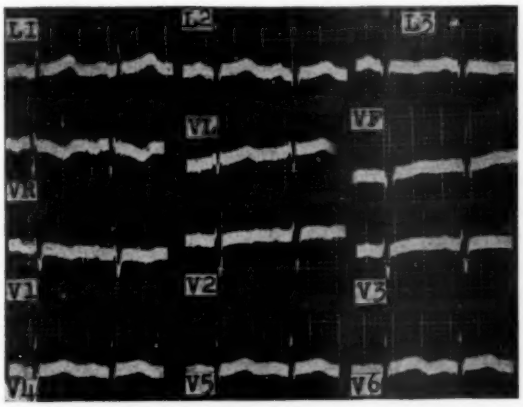

Fig. 7.—Patient F. M. Control tracing (June 21, 1947).

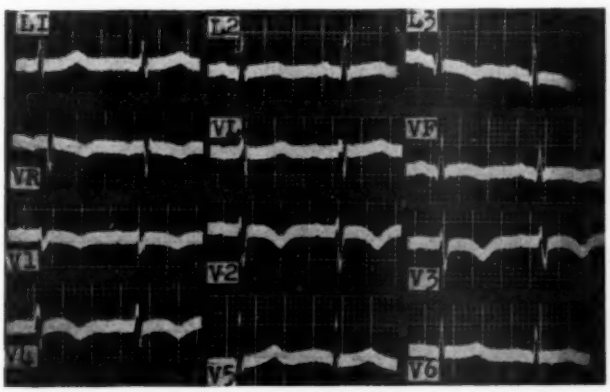

Fig. 8.—Patient F. M. The second tracing, taken after a total dose of 0.60 Gm. (0.01 Gm. per kilogram of body weight; 0.05 Gm. daily). Q-T is prolonged. Treatment was discontinued (July 1, 1947).

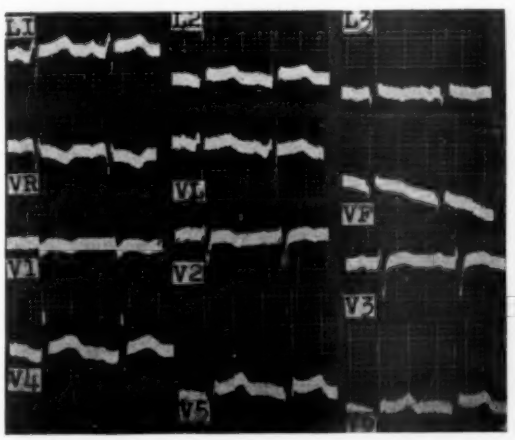

Fig. 9.—Patient F. M. The third tracing, taken fifteen days after the end of the first treatment. T has become positive. Q-T is normal (July 16, 1947).

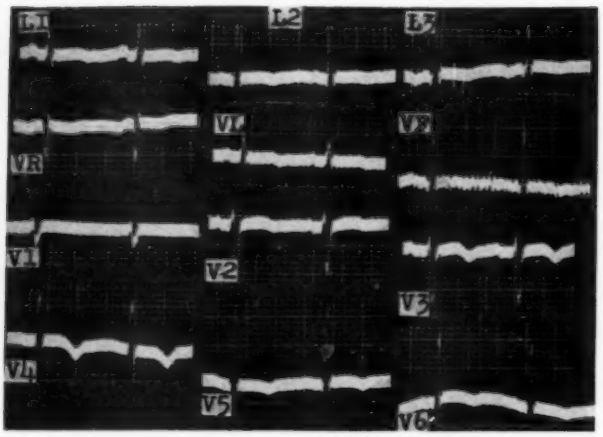

Fig. 10.—Patient F. M. The fourth tracing, taken five days after a second course of emetine therapy was completed. The total dose was 0.55 Gm. T is negative in almost all leads. Q-T is slightly prolonged (Aug. 15, 1947).

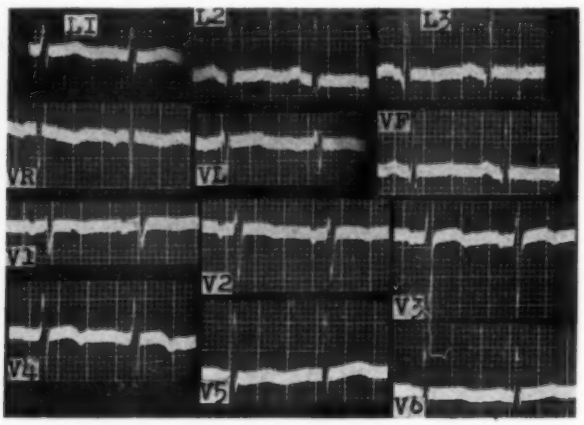

Fig. 11.—Patient F. M. The fifth tracing, taken twenty days after cessation of treatment. T is now positive in I, II, V_3, V_4, V_5, and V_6. Q-T is still prolonged (Aug. 30, 1947).

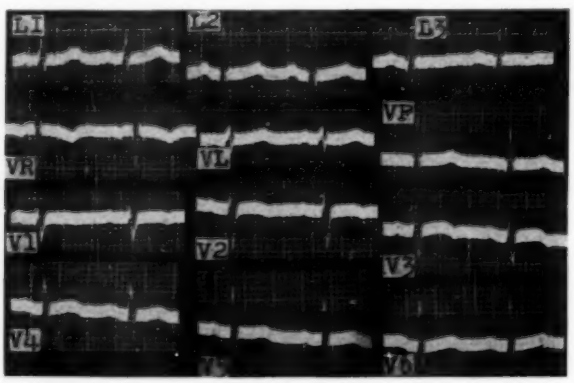

Fig. 12.—Patient F. M. The sixth tracing, taken thirty-eight days after treatment. Record is not necessarily abnormal (Sept. 18, 1947).

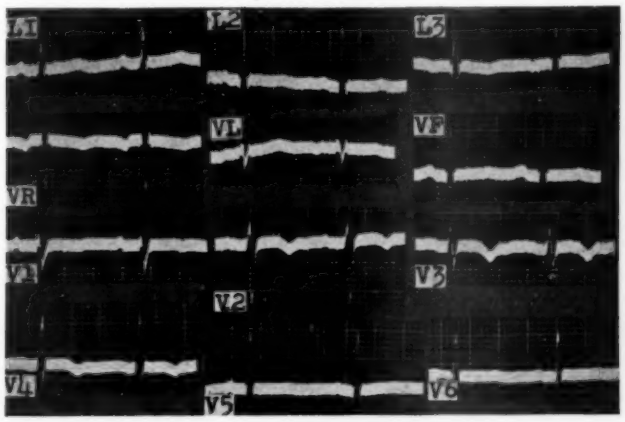

Fig. 13.—Patient F. M. The seventh tracing, taken three days after a third course of treatment was completed (total dose 0.60 Gm.). Electrocardiographic changes are again observed (Oct. 14, 1947).

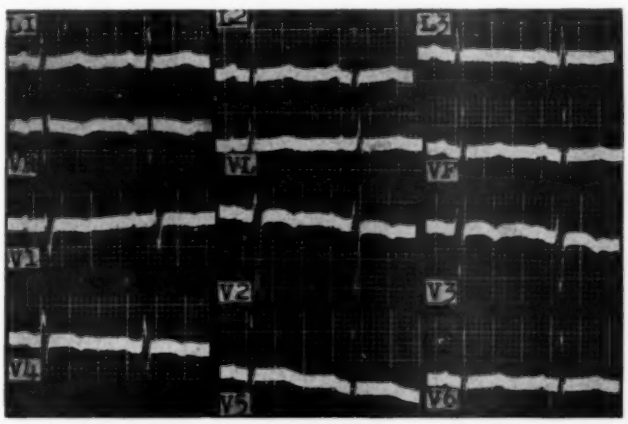

Fig. 14.—Patient F. M. The eighth tracing, taken nineteen days after treatment (third course). Tracing is going back to normal (Oct. 30, 1947).

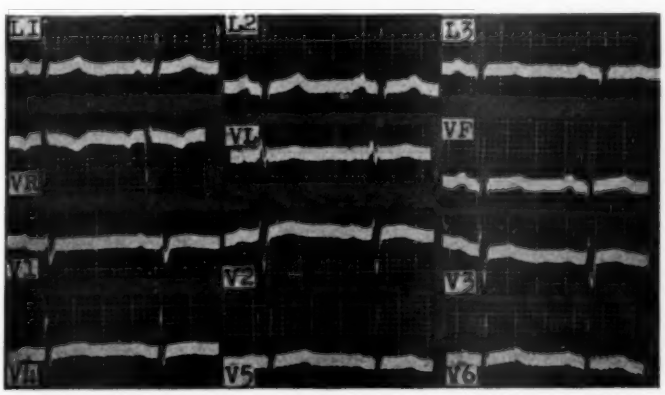

Fig. 15.—Patient F. M. The ninth tracing, taken seventy days after treatment. The electrocardiogram is within normal limits (Dec. 19, 1947).

Of all the observed electrocardiographic changes the most worthy of note is the inversion of the T wave in the precordial leads since it is the first change to appear, the most consistent one (100 per cent), and the last to disappear.

If we take into account that other investigators used only the standard leads, it is easy to understand why they reported a low percentage of electro-

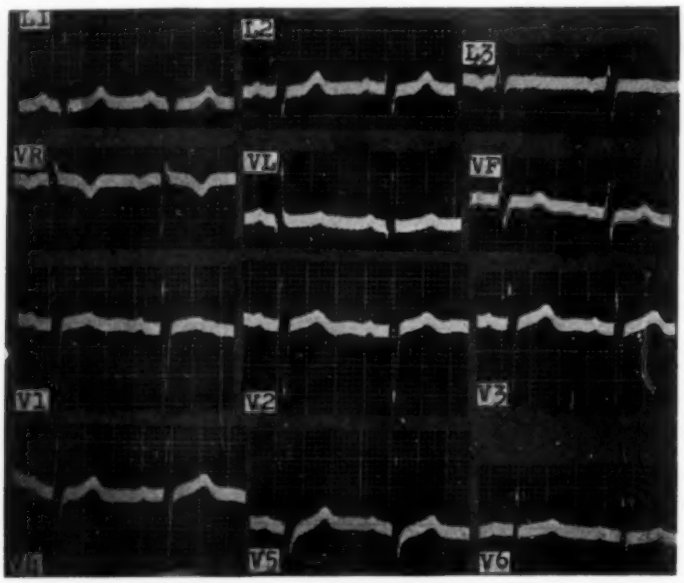

Fig. 16.—Patient P. M. Control tracing; normal record (June 3, 1947).

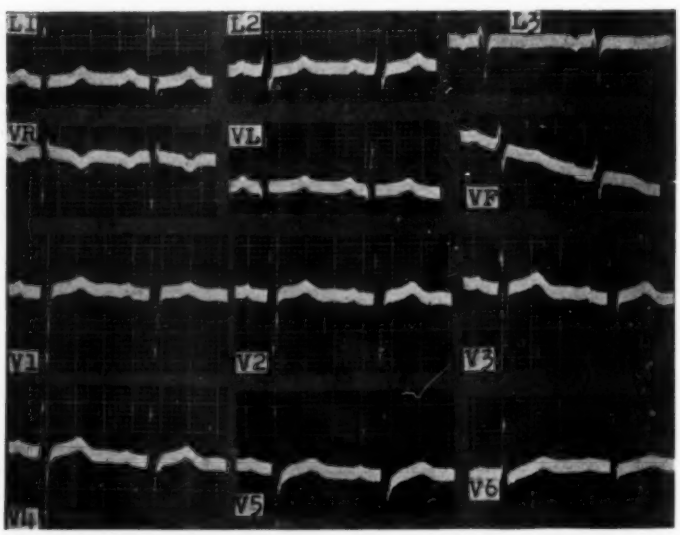

Fig. 17.—Patient P. M. The second tracing, taken after the administration of a total dose of 0.60 Gm. (0.10 Gm. daily). There is a tendency to low voltage of the T wave (June 9, 1947).

cardiographic changes, since in our present study the standard changes occurred in 18 per cent of the cases. Note should be taken that the electrocardiographic changes appeared about seven days after the drug was administered, as pointed out previously by Dack and Moloshok in 1947.[6]

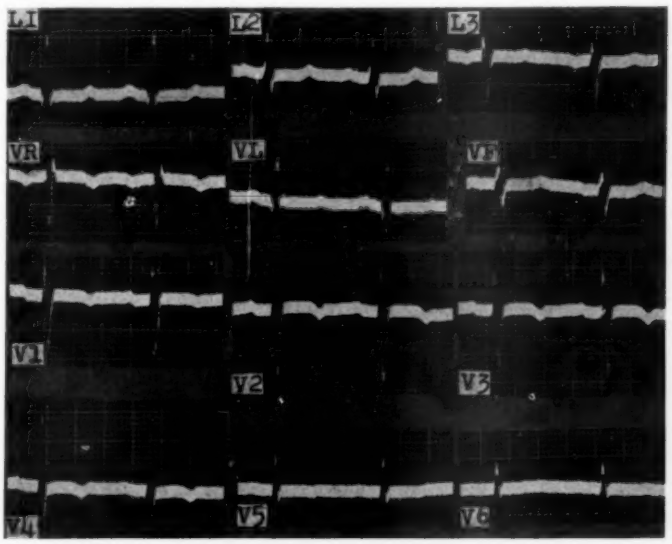

Fig. 18.—Patient P. M. The third tracing, taken after a total dose of 1.50 Gm. (June 18, 1947).

Fig. 19.

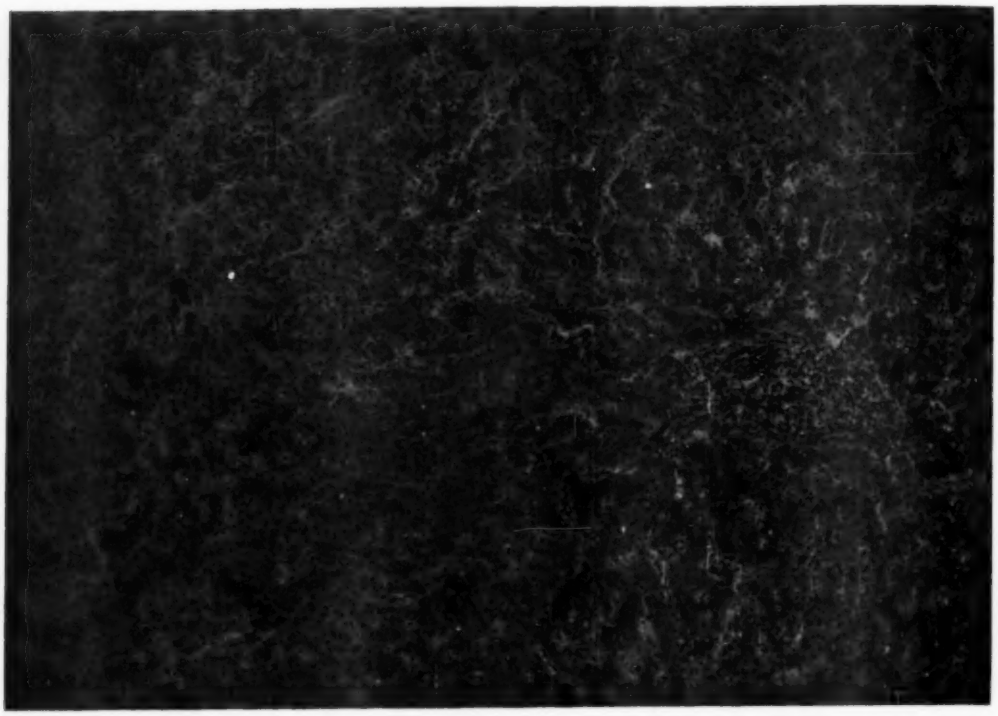

Fig. 20.

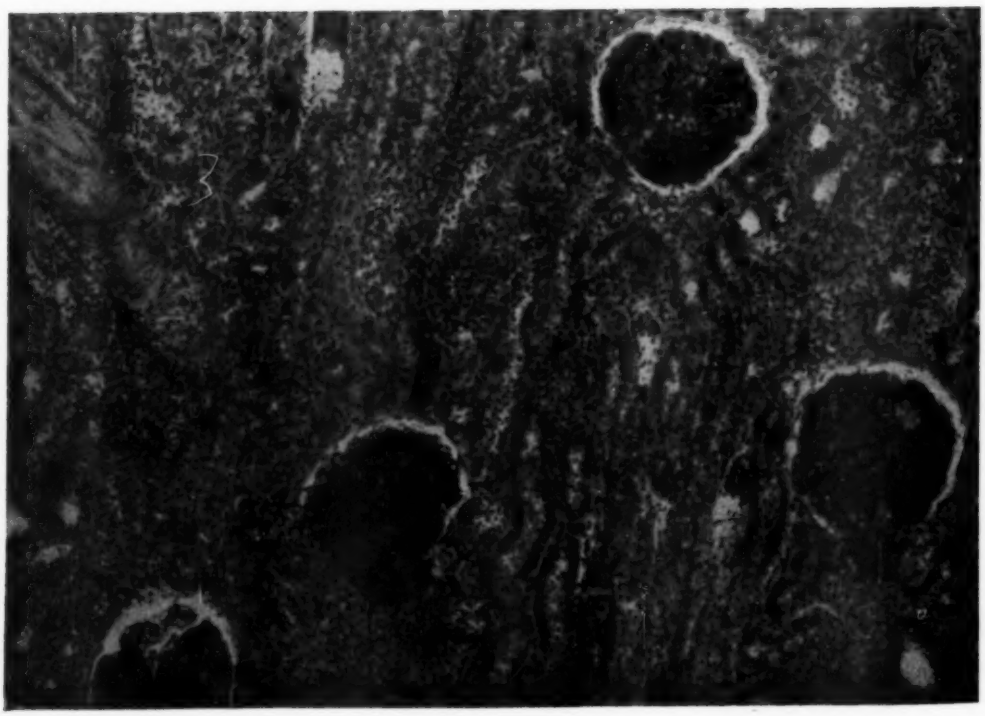

Fig. 21.

The electrocardiographic patterns observed under emetine therapy sometimes resemble those of myocardial infarction, i.e., S-T elevation, T-wave inversion, and prolongation of Q-T.

There are cases in which S-T deviation is not present and only Q-T prolongation and T inversion are observed. In these cases it is rather difficult to establish an accurate electrocardiographic diagnosis if no information about previous treatment is obtained. It is obviously important to be particularly inquisitive about the therapeutics used prior to the electrocardiographic examination, especially in countries where emetine is used in daily practice. Another point to be emphasized is the added hazard of emetine treatment in patients with a history of coronary disease since a toxic drug action will be added to a previously damaged myocardial fiber. The histopathological studies performed in the fatal case reported demonstrate clearly the myocardial damage produced by emetine.

SUMMARY

An electrocardiographic study is presented on forty-five patients undergoing emetine therapy. The route of administration was intramuscular.

The P wave and the ÂP did not reveal significant changes.

The P-R interval was prolonged in only two cases.

ÂQRS showed a right deviation (average 18 degrees) in 62 per cent of the cases and a left deviation (average 28 degrees) in 37 per cent of the cases.

ÂT was deviated to the right (average 25 degrees) in 27 per cent of the cases and to the left (average 44 degrees) in 72 per cent of the cases.

The ventricular gradient did not show significant changes.

The main morphological changes were those seen in the T wave of the precordial leads (inversion in 100 per cent of the cases). Second in importance was the Q-T prolongation (90 per cent of the cases). All the electrocardiographic changes were reversible. The average time required for the complete return of the tracing was over six weeks.

Mention is made of a patient who died because of an accidental overdose of emetine. Photomicrographs of sections of the heart, liver, and kidneys are presented. A correlation is made between the electrocardiographic and pathological changes observed.

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Clinical Reports

COEXISTENT RHEUMATIC FEVER AND SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH ACTH AND ANTIBIOTICS

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EXPERIENCE with ACTH and cortisone in various pathological conditions has been the only valid means of judging their therapeutic effectiveness and will continue to be the touchstone until the mechanism of action is clarified. The use of ACTH in the treatment of acute rheumatic fever with severe heart involvement has been described recently.[1,2,3] To our knowledge no one has as yet described the use of ACTH or cortisone in a case of acute rheumatic fever with coexistent subacute bacterial endocarditis. The following is such a case.

CASE REPORT

History of Present Illness.—The patient is a 23-year-old white man with four months of Army service, who was admitted to the hospital on Feb. 7, 1951, with the following history. He was born in Kentucky and spent the first seventeen years of his life there before moving to Chicago with his parents. At the ages of 12 and 16 years, he suffered from migratory joint pains which persisted for a full year on each occasion. Weakness was present at these times, but he did not feel sick enough to see a physician, and at no time prior to his entry into the service had he ever consulted a physician. Upon induction into the Army, nothing was said to him about the presence of any heart murmur.

He had much difficulty during basic training with palpitation and shortness of breath. Two months prior to admission, he had had two teeth extracted under local anesthesia and had considerable bleeding following the extractions. A month after this he was treated in one of the dispensaries for fever of unknown origin and was given one injection of penicillin. It was noted that wheals appeared locally shortly after the time of administration. They were raised, erythematous, and very itchy, but disappeared within one day. This was the first time he had ever received penicillin. During the month before admission he suffered from easy fatigue, anorexia, and a 10 to 15 pound weight loss. He felt feverish on several occasions, but had no night sweats. Sometimes on arising he felt dizzy.

Four days prior to admission, he suffered sudden, severe pain in both hips. The day prior to admission he experienced pain in most of the other joints, some of which became warm, red, and swollen. For these reasons he was admitted.

Past History.—The past history was otherwise negative.

Family History.—His mother, 47 years old, has rheumatic heart disease. His father and six siblings are alive and well and have no history of rheumatic disease.

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The opinions set forth in this article are those of the authors alone and do not in any way reflect the official policy of the Army Medical Service.

Received for publication June 9, 1951.

Physical Examination on Admission.—The temperature was 102° F, the pulse 120 per minute, the blood pressure 110/70 mm. Hg. He looked chronically and acutely ill, was pale, and showed evidence of recent weight loss. There was marked swelling, redness, and increased temperature of the left elbow, right wrist, and right ankle and extreme tenderness in both knees without much local heat or swelling. There was no evidence of involvement of spine or neck. There was also tenderness and swelling of the right fifth metacarpophalangeal joint. There was no cyanosis or edema. There were twenty to thirty bright red petechiae in each anterior axillary fold. The neck was supple. The eye grounds were perfectly clear. There were no petechiae on the conjunctivae nor on the mucous membranes of the mouth. The tongue was of the so-called strawberry type. The pharynx was slightly reddened. There was no adenopathy. The lungs showed a few râles at the posterior bases, more on the left side than on the right. The heart was apparently enlarged to the left with the point of maximum impulse being felt and seen in the fifth intercostal space just inside the anterior axillary line. A thrill was felt at the apex. The sounds were regular and forceful. The first mitral sound was high pitched and snapping, shorter and louder than the second mitral sound. The second pulmonic sound was greater than the second aortic. At the mitral area there was a presystolic crescendo murmur continuous with a decrescendo, rough, systolic murmur. The presystolic murmur was coincident with the palpable thrill. A faint, systolic, soft, blowing murmur was heard at the aortic area and was poorly transmitted. No gallop rhythm or friction rub was heard. The spleen tip was felt on inspiration.

Admission Laboratory Data.—There was an anemia of 11.5 Gm. of hemoglobin; the white count was 11,000 with a normal differential and a sedimentation rate (Wintrobe) corrected to 32. The hematocrit was 36 per cent. The urine showed one plus albumin with a specific gravity of 1.027. The sediment showed occasional coarsely granular casts and five to six white blood cells per high-power field. The serology was negative. A roentgenogram of the chest showed several miliary calcifications throughout both lung fields. The heart appeared normal in both size and shape (Fig. 1). The electrocardiogram was not remarkable with the exception of a sinus tachycardia and some notching of the T waves in Lead II.

Course in the Hospital.—Upon admission the patient was placed in an oxygen tent. Sodium salicylate, 10 grains, was given every four hours for four doses. Blood cultures were taken four times daily. On the third hospital day it was observed that the heart sounds were changing. A decrescendo, high-pitched, blowing, diastolic murmur was now heard at the apex. This murmur started immediately after the second sound and filled almost the entire diastolic period. The murmur of mitral stenosis was still present, but the systolic murmur was now more prolonged and rough. He was started on ACTH 25 mg. every six hours for the first day, and then every eight hours thereafter, until the dosage was successively reduced. He therefore received 100 mg. for the first day and 75 mg. per day for the next six days, 50 mg. per day for the next five days, and 25 mg. per day for the last six days. This constituted a total of 950 mg. in seventeen days. He was placed on a 1,200 calorie, low-salt diet and given potassium chloride, 2 Gm. daily by mouth. He was placed on the regular diet at the end of ACTH therapy, and the potassium chloride was discontinued during the second hospital week.

On the fourth hospital day the patient was considerably improved. Temperature was now 100° F., pulse 100 per minute, and blood pressure 115/75 mm. Hg. He appeared less toxic, and the redness had left the involved joints, with considerable decrease in swelling. He was able to move them with more freedom and much less pain. The heart tones and murmurs were the same as the day before with the addition of a protodiastolic gallop heard and felt at the apex. The diastolic thrill had disappeared. The blood culture showed early growth, and he was started on 100,000 units of aqueous penicillin every three hours.

On the fifth hospital day he felt better than he had at any time during the past two months. All joint symptoms had disappeared. The joints were completely mobile and normal in appearance. The pulse rate was now 72. The temperature had returned to normal levels. The appetite had improved. No further petechiae were observed. The protodiastolic gallop was not heard, but the systolic and diastolic murmurs now filled both cardiac cycles and were continuous with only a change in pitch recording the points where the murmurs changed from the systolic to the diastolic phase and back again. The following day the decrescendo, diastolic, blowing murmur could not

be heard, whereas the presystolic accentuation at the mitral area was still noted. The protodiastolic gallop had reappeared. There was no significant change in the blood pressure or heart rate. At this time a gram-positive staphylococcus was isolated from two of the early blood cultures.

During the next week the heart murmurs changed almost daily. The decrescendo, high-pitched, blowing, diastolic murmur, heard at the apex, would disappear and appear on daily examinations. The protodiastolic gallop could be heard almost every day and on several occasions could be felt at the apex. The mitral systolic murmur varied in pitch and character, from soft and blowing to loud and rough. On two occasions a high-pitched, whistling, early, systolic murmur was superimposed on this basic systolic pattern. The presystolic accentuation was always present. Frequently it was impossible to hear the first mitral sound due to the intensity of these murmurs. The sounds over the aortic area were normal while the second pulmonic sound was accentuated.

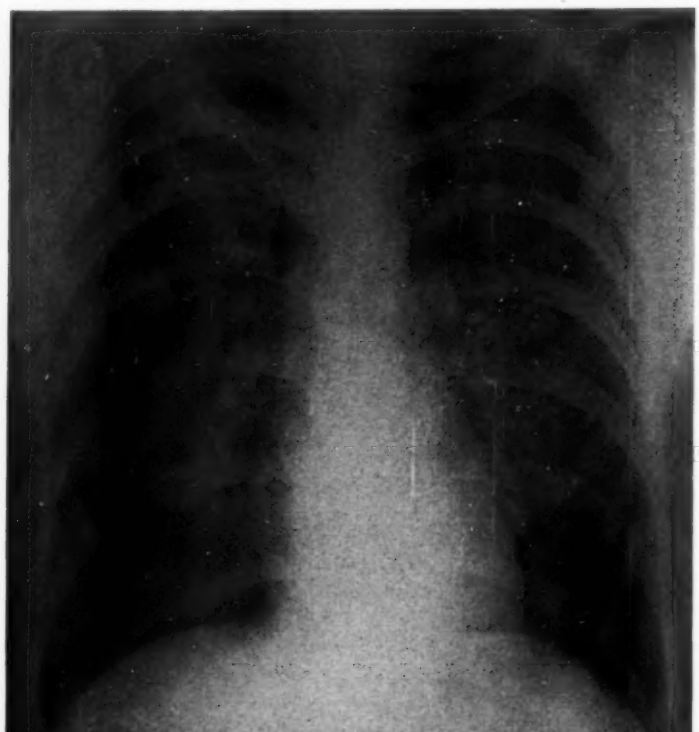

Fig. 1.—Chest roentgenogram. Several healed miliary calcifications were seen throughout both lung fields. The heart was normal in size and shape and did not change under ACTH therapy.

Complete studies on the organism found in the blood cultures were as follows: It was identified as a gram-positive nonhemolytic *Staphylococcus aureus*, completely resistant to aureomycin and sulfadiazine. It was inhibited by 17.5 units per cubic centimeter of aqueous penicillin and was sensitive to a combination of 8 μg of streptomycin and Chloromycetin.*

On the tenth hospital day, he was started on 2 Gm. of streptomycin and 3 Gm. of Chloromycetin per day in divided doses. The penicillin was discontinued. Streptomycin was given 0.5 Gm. intramuscularly every six hours, while the Chloromycetin was given 250 mg. orally every two hours. He therefore received specific antibiotic therapy, starting on the eighth day of ACTH therapy and eight days before its completion.

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From the start of the third day of ACTH treatment, and subsequently, he was afebrile and completely asymptomatic. From the thirteenth hospital day, the heart was regular with a rate varying between 70 and 90, and the blood pressure remained stable at 110/70 mm. Hg. No abnormal thrills were felt; the gallop disappeared and did not return. The heart sounds became stable, the first mitral sound being somewhat higher in pitch than the second sound and not as snapping as on admission. The second pulmonic sound remained slightly accentuated. The presystolic mitral murmur was always heard, and the systolic mitral murmur varied from very soft to moderately loud and rough, being loudest in the upright position. Further petechiae were never demonstrated, and the spleen was not palpable after the first day.

On the fifteenth hospital day, while the patient was still on ACTH therapy, it was noted that there was a typical, although rather pale, urticarial wheal over the inner aspect of the right thigh. This caused considerable pruritis, but only lasted for about four hours. Moreover, it was noted that the intracutaneous histoplasmin skin test was positive at the end of forty-eight hours. These skin manifestations appeared in spite of the fact that he was receiving adequate ACTH therapy as judged by the daily eosinophil counts.

Summary of Pertinent Laboratory Data.—The white count returned to normal shortly after admission and ranged thereafter between 5,000 and 7,000 cells per cubic millimeter. The blood eosinophil count was 110 per cubic millimeter prior to ACTH therapy. Four hours after the initial dose of ACTH, it fell to 66 per cubic millimeter. Thereafter the daily blood eosinophils varied between 80 and 190 per cubic millimeter. On the first day after ACTH was stopped, the eosinophil count was 240, the second day it was 420, and for the following five days it remained between 500 and 600 per cubic millimeter. The fasting blood sugar remained at normal levels during ACTH therapy, while the carbon-dioxide combining power rose from 36 to 51 volumes per cent, and the serum sodium rose slightly from 350 to 376 mg. per cent. The blood potassium did not change, while the blood chloride fell from 491.0 to 461.0 mg. per cent. The total protein fell from 7.7 Gm. per cent to 7.3, while the albumin/globulin ratio fell from 1.3 to 1.0. Glycosuria did not develop at any time, and further albuminuria was not noted. Microscopic hematuria was never found. The urinary uric acid increased from the pretherapy level of 5.6 mg. to 424.0 mg. per specimen. The urinary creatinine concomitantly rose from 5.98 mg. per cent to 106.0 mg. per cent during treatment. (The uric acid and creatinine were measured on the same urinary specimen which was collected between the hours of 9 and 12 in the morning.) This represented a huge increase in the urinary output of both of these metabolites and a fourfold increase in the ratio of uric acid to creatinine. Daily electrocardiographic studies revealed no prolongation of the P-R interval at any time nor evidence of electrolyte disturbance (Fig. 2). A roentgenogram of the chest taken at the end of ACTH therapy was unchanged. The sedimentation rate rose from the admission level of 32 mm. to 50 mm. per hour on the third hospital day and thereafter fell slowly to 20 mm. per hour at the end of three weeks. One further blood culture showing the previously identified organism was found positive while the patient was receiving penicillin and ACTH. A total of nine blood cultures was taken, and they have remained negative since the start of specific antibiotic therapy.

DISCUSSION

The ACTH appeared to be of definite value in the amelioration of the polyarthritis, fever, and general toxicity of the rheumatic fever, and the severe carditis stabilized sooner than might be expected under routine salicylate therapy. Due to the history suggestive of rheumatic fever, this incident may be considered in the nature of a recurrence. The origin of the bacterial endocarditis most probably dated from the dental extraction.

From the onset of ACTH therapy, no further petechiae appeared, and all clinical evidence of septicemia disappeared, although bacteriological evidence persisted until specific therapy was begun. This gives further weight to the

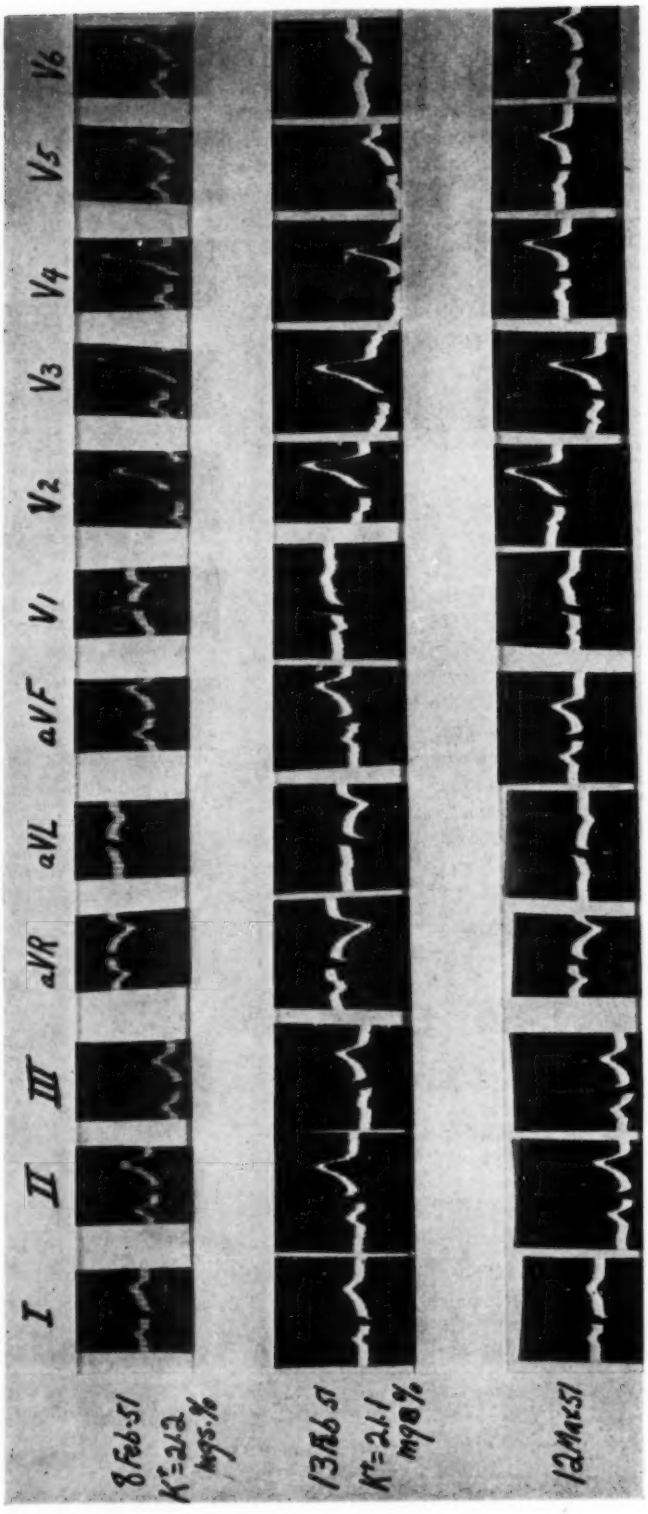

Fig. 2.—Electrocardiograms taken prior to ACTH therapy, on the fourth day of ACTH therapy, and two weeks after completion of ACTH therapy. At no time was there any evidence of electrolyte disturbance.

admonition of Rhoads[4] that ACTH therapy is hazardous in an acute bacterial infection without specific antibiotic therapy. Yet it would also seem that by the suppression of toxicity and the establishment of total well-being, ACTH removes the distressing factor of urgency and allows complete laboratory characterization of the offending pathogen. Thus, the use of ACTH would be justified even if it did not prevent the mutilating scarring seen in healed bacterial endocarditis. As no deleterious effect was noted, further trial with ACTH in subacute bacterial endocarditis is indicated.

SUMMARY

1. A case of acute rheumatic fever with severe carditis coexisting with a bacterial endocarditis has been reported.

2. The causative organism of the subacute bacterial endocarditis was a nonhemolytic *Staph. aureus*, resistant to aureomycin and sulfadiazine, sensitive to 17.5 units of penicillin, and completely inhibited by a combination of 8 μg of Chloromycetin and streptomycin.

3. Treatment was with ACTH, Chloromycetin, and streptomycin. The ACTH appeared to be beneficial to the rheumatic fever and carditis and of possible value in the bacterial endocarditis as an interval measure until the causative organism could be determined.

4. Incidental findings were calcific pulmonic lesions considered to be of histoplasma origin and a penicillin sensitivity that exhibited minimal allergic manifestations probably inhibited by the concomitant ACTH therapy.

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SUBACUTE STAPHYLOCOCCUS AUREUS ENDOCARDITIS: RECOVERY FOLLOWING COMBINED ANTIBIOTIC THERAPY

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STAPHYLOCOCCUS AUREUS endocarditis has been identified most often with an acute fulminating course nearly always fatal. This manifestation of staphylococcal sepsis is usually an incident in a generalized pyemia resulting from some focal infection elsewhere in the body. Only in rare instances has this organism been responsible for a subacute form of endocarditis in which it has implanted itself on a valve previously damaged by rheumatic fever. Our patient, reported herewith, merits inclusion in this group.

CASE REPORT

R. W., a 22-year-old Negro man, was admitted to St. Philip Hospital of the Medical College of Virginia Hospital Division on Sept. 24, 1949. He complained chiefly of severe constant pain in the left upper abdominal quadrant and left shoulder. It had been present for at least twenty-four hours and was unaccompanied by cough, sputum, nausea, vomiting, change in bowel habits, or dysuria. During the week prior to admission he had experienced transient pain in the right calf, left hand, and right fifth finger. There had been fever but no chills. Joint swelling, petechiae, and hematuria had not been observed.

The past history revealed an attack of severe rheumatic fever at the age of 13 years necessitating twelve months of bed rest. He had been a patient in this hospital in 1947 for acute appendicitis. Appendectomy was performed successfully. Penicillin in a daily dose of 200,000 to 400,000 units was given by intermittent intramuscular injection postoperatively. Examination of the heart on this admission disclosed chronic rheumatic valvular disease with cardiac enlargement and mitral and aortic lesions. Hospital discharge occurred six days after operation.

On physical examination the patient was found to be well developed, well nourished, and in no acute distress. The temperature was 100.2° F., the pulse 84, the blood pressure 130/20 mm. Hg. There were no petechiae. The heart was considerably enlarged. Murmurs typical of mitral stenosis and insufficiency and aortic stenosis and insufficiency were present. The rhythm was regular. There was no evidence of congestive failure. The lungs were clear. Tenderness was elicited in the left upper quadrant of the abdomen, and pain was referred to the left shoulder, but the spleen could not be felt. Fingers and toes were clubbed. There was no abnormality of the peripheral joints. The neurological examination was negative.

Laboratory studies disclosed a red blood cell count of 4,000,000 and 10.4 Gm. of hemoglobin. The leukocytes numbered 7,200, 73 per cent being polymorphonuclears. Sedimentation rate was 25 mm. in one hour (Cutler). Chest roentgenogram confirmed the impression of generalized cardiac enlargement which was predominantly of an aortic configuration. The cardiothoracic ratio was 64 per cent. The electrocardiogram indicated myocardial damage, left ventricular hypertrophy, and questionable left bundle branch block (Q-S 0.10 to 0.12 second). A stethogram was

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consistent with a diagnosis of mitral and aortic stenosis and insufficiency. A roentgenogram of the abdomen failed to demonstrate hepatic or splenic enlargement. A blood culture obtained on the day following admission was positive for *Staph. aureus*.

The initial positive culture was considered most likely a result of contamination, and a tentative diagnosis of acute rheumatic fever was made. The course was febrile, the temperature being irregular and fluctuating between normal and 103° F. On the fifth hospital day there was pain and tenderness in the tip of the left fourth finger for twenty-four hours, but there was no redness or swelling. Salicylate therapy in dosage sufficient to produce a blood level of 10 to 16 mg. per cent was without effect on the fever. During this period no petechiae were observed, and there was no anemia or hematuria. The total leukocyte count did not exceed 12,200. Sternal marrow study on Oct. 10, 1949, was reported as follows: "There is slight hyperplasia of myeloid cells. Eosinophils, plasma cells, and megakaryocytes are increased. Most of the megakaryocytes appear disintegrated. There appears to be marked platelet production." A smear of the peripheral blood examined* on Oct. 14, 1949, revealed the presence of macrophages of the reticuloendothelial system which have been described in cases of subacute bacterial endocarditis.

Between September 25 and October 12 a total of fourteen blood cultures was taken. Thirteen of these were positive for the identical staphylococcus isolated initially. Culture of the sternal marrow was similarly positive. The organism was found to be coagulase positive and was agglutinated by the patient's serum in a dilution of 1:160. Laboratory tests indicated that it was highly resistant to penicillin, but sensitive to streptomycin in a concentration of less than 0.75 μg per cubic centimeter and to aureomycin in a concentration between 0.18 and 0.375 μg per cubic centimeter.

Despite the subacute nature of the process, it was felt that the evidence strongly favored a diagnosis of *Staph. aureus* endocarditis. Antibiotic therapy was therefore instituted on the nineteenth day (October 13) with dihydrostreptomycin and on the twenty-first day (October 15) with penicillin and aureomycin and was continued for a total of thirty-three days. The treatment regimen consisted of penicillin and dihydrostreptomycin by intermittent intramuscular injection in a daily dosage of 4 million units and 2 Gm., respectively. In addition, 4 Gm. of aureomycin were given by mouth in divided doses during each twenty-four hour period. The temperature promptly returned to normal and did not rise during the remainder of the hospital stay. Between the initiation of treatment and its termination, twenty-two blood cultures were negative, and the sedimentation rate dropped from 25 mm. to 10 mm. in one hour. The patient had no further complaints and appeared well at the time he left the hospital on Nov. 15, 1949.

Following discharge the patient was not seen again until March 20, 1950, at which time there were no complaints. The heart was well compensated. Hematological study was normal, the sedimentation rate being 2 mm. in one hour and the blood culture negative. The electrocardiogram now showed definite left bundle branch block.

In May, 1950, he developed symptoms and signs of congestive failure, but responded satisfactorily to digitalization, diuretics, and salt restriction.

A communication from a New York hospital advised us of his admission there on Feb. 14, 1951, because of congestive failure. There was no evidence of active endocarditis or rheumatic fever. The sedimentation rate was 10 mm. in one hour. The blood studies and urinalysis were normal.

DISCUSSION

This case is unusual from the clinical, bacteriological, and therapeutic standpoints. There is no doubt as to the etiology since multiple blood cultures consistently yielded a coagulase-positive *Staph. aureus*. It appears that this organism was responsible for the development of endocarditis in a patient with chronic rheumatic valvular disease. Arrest of the infection following an intensive course of combined antibiotic therapy apparently has taken place. This assumption is

*By Dr. J. E. Stevens.

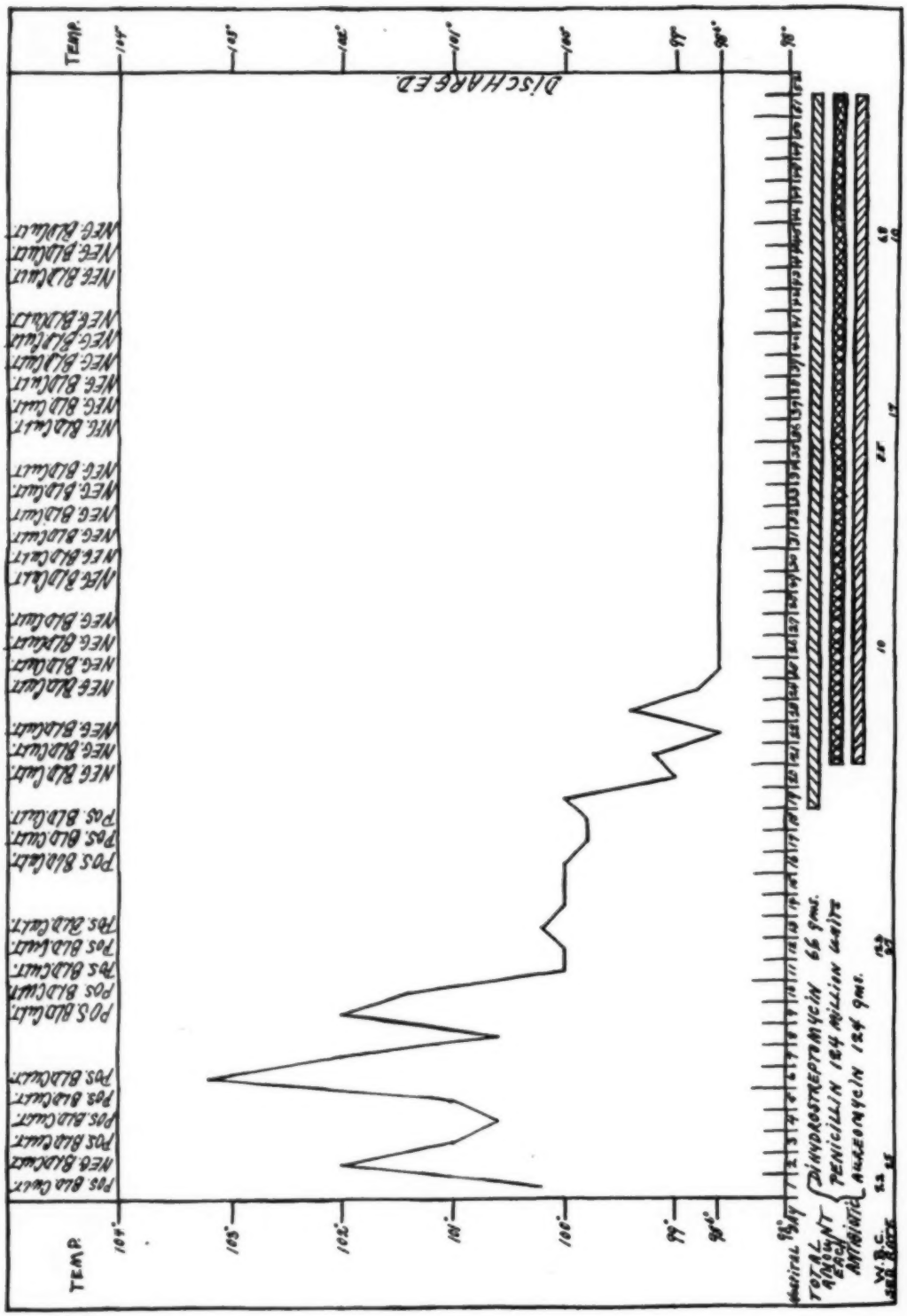

Fig. 1.—Chart of hospital course.

substantiated by the prompt eradication of the organisms from the blood stream and the progressive clinical improvement while under treatment. Further support is gained by the absence of fever, the normal sedimentation rate and blood studies, the normal urine, the negative blood cultures, and the disappearance of finger clubbing when the patient was observed seven months after treatment was completed. Except for two episodes of congestive failure, from each of which prompt recovery ensued, he has remained well and free from relapse of the endocarditis or reinfection for a period of sixteen months.

The increasing frequency with which penicillin-resistant staphylococci are being encountered presents a problem of considerable magnitude.[1-4,7] In disease caused by these bacteria the use of antibiotic combinations may afford the best opportunity for cure. The sensitivity of the staphylococcus responsible for our patient's disease to low concentrations of streptomycin and aureomycin prompted us to administer these two drugs simultaneously. We included penicillin also despite the apparent insensitiveness of the causative agent, since we hoped that the triple combination might have a more potent effect by synergistic action than either streptomycin or aureomycin alone or together. It would appear that the in vivo activity of penicillin cannot always be predicted on the basis of in vitro tests. According to Tumulty and Harvey,[5] an apparently resistant organism may respond satisfactorily to an average dose of penicillin. In this connection we are reminded of a case of subacute bacterial endocarditis in a young Negro woman seen by one of us (W. H. H.).[6] Though the organism, a strain of *Streptococcus viridans*, proved resistant except in a penicillin concentration varying between 25 and 50 units per cubic centimeter, she recovered on a daily dosage of 2,400,000 units administered by intermittent intramuscular injection for forty-one days and had remained well when observed twelve months later. Though serum penicillin determinations were not made, previous experience indicates that levels of 25 to 50 units per cubic centimeter cannot be attained on the dosage employed.

Fig. 1.—Chart of hospital course.

Cases similar to the one reported, with their hopeless prognosis and low recovery rate even after optimum penicillin therapy, justify the use of large doses of antibiotic drugs in combination. Because of possible synergistic action, we believe that penicillin should be a part of the treatment regimen in all cases of endocarditis due to a gram-positive coccus, even though the results of in vitro sensitivity tests may indicate a high degree of resistance.

SUMMARY

1. A case of subacute bacterial endocarditis due to a penicillin-resistant, coagulase-positive *Staph. aureus* superimposed on chronic rheumatic valvular disease has been reported.

2. Combination antibiotic therapy consisting of the simultaneous administration of penicillin, dihydrostreptomycin, and aureomycin for thirty-three days resulted in prompt clearing of the blood stream, progressive improvement, and the absence of any evidence of active infection when the patient was examined seven and sixteen months later.

3. Treatment of similar cases with large doses of antibiotic drugs in combination is suggested.

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Book Reviews

ANGIOCARDIOGRAPHY (Annals of Roentgenology, Vol. XX). By Charles T. Dotter, M.D., and Israel Steinberg, M.D. New York, 1951, Paul B. Hoeber, Inc.

This is an excellent monographic atlas devoted exclusively to angiocardiography. The book is profusely illustrated with prints of roentgenographic studies showing contrast material in the cardiac chambers of normal subjects and cardiac patients. Shaded diagrammatic figures aid in the interpretation of the x-ray figures shown.

The first four chapters are devoted to a discussion of the techniques and equipment employed and to an evaluation of the contrast media used. These will probably be of interest mainly to the roentgenologist actively engaged in such work. Of special interest is the section on mortality in angiocardiography, including a consideration of the mechanism of fatalities. The authors stress the danger of the procedure in the cyanotic child. The illustrations of the normal angiocardiogram are especially clear and demonstrate the normal cardiac chambers well.

The remaining chapters deal with acquired heart disease, congenital heart disease (cyanotic and noncyanotic), and pulmonary disease, including pulmonary tumors. The diagnostic aid to be derived from such studies is well proved in many instances, but would appear to be highly questionable with some types of heart disease, an admission freely concurred in by the authors. The limitations of the method and the need for the additional help given by cardiac catheterization in many patients are also pointed out. In general, however, the help to be derived from such studies in various types of cardiac, aortic, and pulmonary disease is clearly illustrated by this volume. Clinicians interested in these fields will benefit from a perusal of this monograph.

H.E.H.

THE APPROACH TO CARDIOLOGY. By Crighton Bramwell, M.A., M.D., F.R.C.P. London, 1951, Oxford University Press, 122 pages. Price $3.75.

This volume is based on a series of lectures which the author gave to bridge for the student the transition from the preclinical to the clinical years. The author, in view of his great interest in both heart disease and physiology, is pre-eminently fitted for the task of showing how the information acquired in the early years can be logically applied to the study of patients.

This is not a textbook on cardiology, but a great deal of valuable information is contained in a small amount of space. Although the book deals only with cardiology, the same philosophy could be applied to any other branch of medicine.

It can be most heartily recommended to all medical students beginning the study of clinical medicine and also to those teachers whose duty it is to instruct them during this period.

J.H.C.

NUEVAS BASES DE LA ELECTROCARDIOGRAFIA. By Demetrio Sodi-Pallares, M.D., Mexico, D.F., 1951, La Prensa Medica Mexicana, 624 pages.

This book is an astounding collection of theoretical and practical facts of electrocardiography combined with the author's own experimental data and clinical observations in the form of a well-connotated text on the subject.

Sodi-Pallares begins his book by explaining in simple, everyday terms the fundamental principles of the science of electrocardiography, not only from the viewpoint of the electrophysiology of the heart, but also from the chemical, physical, and mathematical points of view.

After this review of the fundamentals, he presents a well-organized discussion of the electrocardiographic findings, normal and abnormal, in the limb and precordial leads.

He then discusses clearly the more complex problems of electrocardiography, such as vectorcardiography and the formation of the ventricular gradient, in a concise manner.

This text, which was designed for the medical student, is excellent also for practitioners and for specialists in the field of electrocardiography.

Although presented only in Spanish, it is remarkably easy to read for the elementary student of the Spanish language, and every word contributes to the reader's knowledge of the subject.

G.H.C.H.

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